

Exhibit 1



U.S. Food & Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
www.fda.gov

Scientific Review of Modified Risk Tobacco Product Application (MRTPA) Under Section 911(d) of the FD&C Act – Technical Project Lead

SUBMISSION INFORMATION			
Applicant	Philip Morris Products S.A.		
Product Manufacturer	Philip Morris Products S.A.		
Submission Date	November 18, 2016	FDA Receipt Date	December 5, 2016
Purpose	<input checked="" type="checkbox"/> Risk Modification (911(g)(1)) order <input checked="" type="checkbox"/> Exposure Modification (911(g)(2)) order		
Proposed Modified Risk Claims	<p>Modified Risk Claim #1: "AVAILABLE EVIDENCE TO DATE: • The IQOS system heats tobacco but does not burn it. • This significantly reduces the production of harmful and potentially harmful chemicals. • Scientific studies have shown that switching completely from conventional cigarettes to the IQOS system can reduce the risks of tobacco-related diseases."</p> <p>Modified Risk Claim #2: "AVAILABLE EVIDENCE TO DATE: • Switching completely to IQOS presents less risk of harm than continuing to smoke cigarettes."</p> <p>Modified Risk Claim #3: "AVAILABLE EVIDENCE TO DATE: • The IQOS system heats tobacco but does not burn it. • This significantly reduces the production of harmful and potentially harmful chemicals. • Scientific studies have shown that switching completely from conventional cigarettes to the IQOS system significantly reduces your body's exposure to harmful or potentially harmful chemicals."</p>		
PROPOSED MODIFIED RISK TOBACCO PRODUCT (SINGLE PRODUCTS)			
MR0000059: Marlboro Heatsticks¹			
Product Category	Cigarettes		
Product Sub-Category	Non-Combusted		
Package Type	Box		
Package Quantity	20 Heatsticks		
Characterizing Flavor	None		
Length	45 mm		
Diameter	7.42 mm		

¹ May be sold individually or as a co-packaged product.

Ventilation	Not Applicable ²
Source of Energy	Electric (rechargeable battery) ³
MR0000060: Marlboro Smooth Menthol Heatsticks¹	
Product Category	Cigarettes
Product Sub-Category	Non-Combusted
Package Type	Box
Package Quantity	20 Heatsticks
Characterizing Flavor	Menthol
Length	45 mm
Diameter	7.42 mm
Ventilation	Not Applicable ²
Source of Energy	Electric (rechargeable battery) ³
MR0000061: Marlboro Fresh Menthol Heatsticks¹	
Product Category	Cigarettes
Product Sub-Category	Non-Combusted
Package Type	Box
Package Quantity	20 Heatsticks
Characterizing Flavor	Menthol
Length	45 mm
Diameter	7.42 mm
Ventilation	Not Applicable ²
Source of Energy	Electric (rechargeable battery) ³
MR0000133: IQOS System Holder and Charger¹	
Product Category	Cigarettes
Product Sub-Category	Non-Combusted
Package Type	Box
Package Quantity	1 Holder, 1 Charger
Characterizing Flavor	None
Length	93.60 mm (Holder), 112.50 mm (IQOS Charger)
Diameter	15.04 mm (Holder)
Length	112.50 mm (Charger)
Width	51.20 mm (Charger)
Ventilation	Not Applicable ²
Source of Energy	Electric (rechargeable battery) ³
Additional Properties	Depth: 21.86 mm (Charger)
	Battery Capacity: (b) (4) (Holder)
	Wattage: (b) (4) (Charger) ⁴
	Battery Capacity: (b) (4) (Charger)

² For this product neither filter efficiency or ventilation are used to control aerosol deliveries.

³ The components and assemblies control the delivery of energy. The critical items include the (b) (4) (b) (4) including the heating blade and the battery.

⁴ Wattage provided for the charger battery.

Cross-referenced Submissions	Cross-referenced STN	Primary STN(s)
	(b) (4)	APPLIES TO ALL STNs ABOVE
	(b) (4)	
	(b) (4)	

DISCIPLINES REVIEWED**DATE OF REVIEW**

Behavioral/Clinical Pharmacology	June 29, 2020
Chemistry	June 29, 2020
Environmental Science	June 29, 2020
Engineering	June 29, 2020
Epidemiology	June 29, 2020
Medical	June 30, 2020
Microbiology	June 29, 2020
OCE – BIMO	June 30, 2020
OCE – LAB	June 30, 2020
OCE – MFG	June 30, 2020
OCE – DPAL	June 30, 2020
Social Science	June 29, 2020
Statistics	June 29, 2020
Toxicology	June 30, 2020

Recommended Action(s)

Issue a Modified Risk Granted letter under 911(g)(2)
Issue a Modified Risk Denial letter under 911(g)(1)

Technical Project Lead (TPL):

/S/

Benjamin J. Apelberg, Ph.D.
Director
Division of Population Health Science

Signatory Decision:

- ☒ Concur with TPL recommendation and basis of recommendation
- ☐ Concur with TPL recommendation with additional comments (see separate memo)
- ☐ Do not concur with TPL recommendation (see separate memo)

/S/

Matthew R. Holman, Ph.D.
Director
Office of Science

Table of Contents

I.	Executive Summary.....	7
II.	Regulatory Information.....	14
A.	Regulatory History	14
B.	Proposed Modified Risk Tobacco Product	16
1.	Description of Product	16
2.	Proposed Modified Risk Claims.....	16
C.	Tobacco Products Scientific Advisory Committee (TPSAC).....	17
D.	Public Availability of MRTPAs.....	19
III.	Summary of Scientific Evidence	20
A.	Relative Health Risks of the Proposed MRTPs to Individual Tobacco Users.....	20
1.	Combustion	20
2.	Harmful and Potentially Harmful Constituents (HPHCs).....	21
3.	Toxicological Assessment.....	26
4.	Clinical Assessment	33
5.	Assessment of Potential Health Risks to Tobacco Users and Non-Users	40
B.	Consumer Understanding and Perceptions	44
1.	Labels, Labeling, and Advertising (LLA) with Proposed Modified Risk Information	44
2.	Consumer Studies	44
C.	Tobacco Use Behavior and Impacts to the Population as a Whole	52
1.	Impacts to Tobacco Users	52
2.	Impacts to Non-Users of Tobacco	62
3.	Population Health Impact Model (PHIM)	66
IV.	Conclusions and Recommendations	68
A.	Review Conclusions – Risk Modification Order Request	68
B.	Review Conclusions – Exposure Modification Order Request	70
C.	Environmental Impact.....	75
D.	Postmarket Surveillance and Studies (PMSS)	75

Table 1. Chemical testing reported by the applicant to characterize constituent levels in the IQOS System with Marlboro Heatsticks.....	22
Table 2. Human clinical “reduced exposure” (REX) research studies included in the MRTPAs.....	33
Table 3. Biomarkers of exposure (BOEs) measured in REX Studies and their corresponding HPHC, chemical class, and toxicity class	34
Table 4. Surgeon General (SG) warnings and PMI warnings tested in the applicant’s consumer perception studies	45
Table 5. Description of pre- and post-market studies of IQOS use patterns among tobacco users	55
Table 6. Prevalence of Heatstick initiation and switching at study end, by country	57
Figure 1. Components of IQOS Tobacco Heating System	16
Figure 2. Lowest observed genotoxic effect levels for TPM	28
Figure 3. Lowest observed genotoxic effect levels for GVP.....	28
Figure 4. Percent change in BOEs from baseline geometric mean levels (and 95% CIs) at Day 5 in ZRHR-REXC-03-EU (upper panel) and ZRHR-REXC-04-JP (lower panel)	35
Figure 5. Perceived health risks of IQOS and use of other products after viewing IQOS brochure with reduced exposure claim and Surgeon General’s (SG) warnings	47
Figure 6. Percent of all participants in each main IQOS use category at the end of the PBA-07 and Whole Offer Test (WOT) studies, by country	58

I. Executive Summary

Background

On November 18, 2016, Philip Morris Products (PMP) S.A. submitted modified risk tobacco product applications (MRTPAs) for the IQOS system, including the Holder and Charger and three types of Heatsticks: Marlboro Heatsticks, Marlboro Smooth Menthol Heatsticks, and Marlboro Fresh Menthol Heatsticks, which were received by FDA on December 5, 2016. PMP S.A. requested modified risk tobacco product (MRTP) orders under sections 911(g)(1) and 911(g)(2) of the Federal Food, Drug, and Cosmetic Act (FD&C Act).

Under section 910 of the FD&C Act, the applicant requested authorization to market the IQOS system with Marlboro Heatsticks, Marlboro Smooth Menthol Heatsticks, and Marlboro Fresh Menthol Heatsticks without modified risk claims. FDA authorized the marketing of the IQOS system without modified risk claims on April 30, 2019. The technical project lead (TPL) review for the accompanying premarket tobacco product applications (PMTAs) provides detail on the engineering, chemistry, stability, and manufacturing of the products, including the results of FDA inspections of manufacturing sites.⁵ Where relevant, the present review reflects determinations made in the PMTA TPL review.

The focus of this review of the MRTPAs is on the (1) assessment of the proposed modified risk claims, (2) relative health risks of the products, (3) consumer understanding, and (4) potential impact to the population from marketing the products with the proposed modified risk claims. This review separately addresses the risk modification pathway under section 911(g)(1) of the FD&C Act and the exposure modification pathway under section 911(g)(2) of the FD&C Act.

Risk Modification Order Request

The applicant has requested a risk modification order under section 911(g)(1) of the FD&C Act to market these products as follows:

Modified Risk Claim #1:

“AVAILABLE EVIDENCE TO DATE:

- The IQOS system heats tobacco but does not burn it.
- This significantly reduces the production of harmful and potentially harmful chemicals.
- Scientific studies have shown that switching completely from conventional cigarettes to the IQOS system can reduce the risks of tobacco-related diseases.”

Modified Risk Claim #2:

“AVAILABLE EVIDENCE TO DATE:

- Switching completely to IQOS presents less risk of harm than continuing to smoke cigarettes.”

In order for FDA to issue a risk modification order under section 911(g)(1) of the FD&C Act, the applicant must demonstrate that the proposed modified risk tobacco product, as it is actually used by consumers, will:

⁵ The PMTA TPL review is available at: <https://www.fda.gov/tobacco-products/premarket-tobacco-product-applications/premarket-tobacco-product-marketing-orders>

- Significantly reduce harm and the risk of tobacco-related disease to individual tobacco users; and
- Benefit the health of the population as a whole taking into account both users of tobacco products and persons who do not currently use tobacco products.

In evaluating the benefit to health of individuals and of the population as a whole under section 911(g)(1) of the FD&C Act, FDA must take into account:

- The relative health risks the modified risk tobacco product presents to individuals;
- The increased or decreased likelihood that existing tobacco product users who would otherwise stop using such products will switch to using the modified risk tobacco product;
- The increased or decreased likelihood that persons who do not use tobacco products will start using the modified risk tobacco product;
- The risks and benefits to persons from the use of the modified risk tobacco product compared to the use of smoking cessation drug or device products approved by FDA to treat nicotine dependence; and
- Comments, data, and information submitted to FDA by interested persons (section 911(g)(4) of the FD&C Act).

Furthermore, FDA must ensure that the advertising and labeling of the MRTP enable the public to comprehend the information concerning modified risk and to understand the relative significance of such information in the context of total health and in relation to all of the tobacco-related diseases and health conditions (section 911(h)(1) of the FD&C Act).

To the extent possible, the assessment integrates the various threads of evidence regarding the product and its potential effects on health and tobacco use behavior, including tobacco use initiation, to determine both the net effect of the product on overall tobacco-related morbidity and mortality and the distribution of the benefits and harms across the population.

After conducting a thorough scientific review of the information contained in the MRTPAs; the recommendations from the Tobacco Products Scientific Advisory Committee; comments, data, and information submitted to FDA by interested persons; and other scientific information identified by the agency from other sources, I conclude that:

- With respect the risk modification order requests, the applicant **has not demonstrated** that, as actually used by consumers, the products sold or distributed with the proposed modified risk information will significantly reduce harm and the risk of tobacco-related disease to individual tobacco users and benefit the health of the population as a whole, taking into account both users of tobacco products and persons who do not currently use tobacco products.

In particular, I find that the claims “Scientific studies have shown that switching completely from conventional cigarettes to the IQOS system can reduce the risks of tobacco-related diseases.” and “Switching completely to IQOS presents less risk of harm than continuing to smoke cigarettes.” are not substantiated. These reflect the conclusions from reviewers from the four scientific disciplines that

evaluated the modified risk claims (Toxicology, Epidemiology, Medical, and Behavioral and Clinical Pharmacology) and are consistent with the findings from the Tobacco Products Scientific Advisory Committee (TPSAC). Although the available scientific evidence shows that the IQOS system produces lower concentrations of many harmful and potentially harmful constituents (HPHCs) compared to cigarette smoke and the non-clinical data suggests a favorable toxicological profile of the IQOS system compared to combusted cigarettes, the overall body of evidence was not sufficient to demonstrate that completely switching from combusted cigarettes to the IQOS system reduces the risk of tobacco-related disease or harm. Although the non-clinical evidence suggests a lower toxic potential for IQOS, there were limitations in the design of these studies that created uncertainty in the interpretation of study findings, thereby limiting the conclusions that could be drawn from this evidence. In terms of the clinical studies, it should first be noted that the applicant provided no long-term epidemiological data to show risk reduction. Additionally, in the two 90-day clinical studies, the biomarkers of potential harm (BOPHS) measured did not change appreciably across continued smokers, complete switchers to IQOS, and smoking abstinence. The six-month clinical study resulted in some significant differences in BOPHS, but the clinical significance of these changes is unclear. In addition, the proposed claims are exceedingly broad in their reference to “tobacco-related diseases” and “harm” in general, which implicates both claim substantiation and consumer understanding. Cigarette smoking is a cause of many diseases and harms and the relationship between increased consumption and disease risk varies. In addition, the abuse liability of the IQOS system is not expected to be appreciably different than that of combusted cigarettes. Similar abuse liability signifies that the IQOS system can sustain addiction in nicotine-dependent populations and, in non-users, can have a similar risk of initiation and developing addiction as combusted cigarettes. Overall, the evidence is not sufficient to demonstrate substantiation of either of the claims about reduced risk of tobacco-related disease or harm. Relatedly, there is no direct clinical or epidemiological evidence of risk reduction, and the available evidence is insufficient to demonstrate that the product, as actually used by consumers, will significantly reduce harm and risk to individual users and benefit the health of the population as a whole. Thus, the 911(g)(1) order should be denied.

Exposure Modification Order Request

The applicant has also requested an exposure modification order under section 911(g)(2) of the FD&C Act to market these products as follows:

“AVAILABLE EVIDENCE TO DATE:

- The IQOS system heats tobacco but does not burn it.
- This significantly reduces the production of harmful and potentially harmful chemicals.
- Scientific studies have shown that switching completely from conventional cigarettes to the IQOS system significantly reduces your body’s exposure to harmful or potentially harmful chemicals.”

Given the different requirements under sections 911(g)(1) and 911(g)(2), exposure modification orders may be granted by FDA when the available evidence is not sufficient for a risk modification order. Specifically, FDA may issue an exposure modification order under section 911(g)(2) of the FD&C Act (the “special rule”) if it determines that the applicant has demonstrated that:

- Such an order would be appropriate to promote the public health;
- Any aspect of the label, labeling, and advertising for the product that would cause the product to be a modified risk tobacco product is limited to an explicit or implicit

representation that the tobacco product or its smoke does not contain or is free of a substance or contains a reduced level of a substance, or presents a reduced exposure to a substance in tobacco smoke;

- Scientific evidence is not available and, using the best available scientific methods, cannot be made available without conducting long-term epidemiological studies for an application to meet the standards for obtaining an order under section 911(g)(1); and
- The scientific evidence that is available without conducting long-term epidemiological studies demonstrates that a measurable and substantial reduction in morbidity or mortality among individual tobacco users is reasonably likely in subsequent studies (section 911(g)(2)(A) of the FD&C Act).

Furthermore, for FDA to issue an exposure modification order, FDA must find that the applicant has demonstrated that:

- The magnitude of overall reductions in exposure to the substance or substances which are the subject of the application is substantial, such substance or substances are harmful, and the product as actually used exposes consumers to the specified reduced level of the substance or substances;
- The product as actually used by consumers will not expose them to higher levels of other harmful substances compared to the similar types of tobacco products then on the market unless such increases are minimal and the reasonably likely overall impact of use of the product remains a substantial and measurable reduction in overall morbidity and mortality among individual tobacco users;
- Testing of actual consumer perception shows that, as the applicant proposes to label and market the product, consumers will not be misled into believing that the product is or has been demonstrated to be less harmful, or presents or has been demonstrated to present less of a risk of disease than one or more other commercially marketed tobacco products; and
- Issuance of the exposure modification order is expected to benefit the health of the population as a whole taking into account both users of tobacco products and persons who do not currently use tobacco products (section 911(g)(2)(B) of the FD&C Act).

In making the determinations under section 911(g)(2) of the FD&C Act, FDA must take into account:

- The relative health risks the modified risk tobacco product presents to individuals;
- The increased or decreased likelihood that existing tobacco product users who would otherwise stop using such products will switch to using the modified risk tobacco product;
- The increased or decreased likelihood that persons who do not use tobacco products will start using the modified risk tobacco product;
- The risks and benefits to persons from the use of the modified risk tobacco product compared to the use of smoking cessation drug or device products approved by FDA to treat nicotine dependence; and

- Comments, data, and information submitted to FDA by interested persons (section 911(g)(4) of the FD&C Act).

In short, unlike the section 911(g)(1) standard, which requires scientific evidence showing actual risk reduction (e.g., a finding that the product, as actually used by consumers, *will significantly reduce* harm and risk to individual users; a finding that the product, as actually used by consumers, *will benefit* the health of the population as a whole), section 911(g)(2) establishes a lower standard, which allows FDA to issue an order when risk reduction has not yet been demonstrated but is reasonably likely based on demonstrated reductions in exposure (e.g., a finding that a reduction in morbidity or mortality among individual users is *reasonably likely* in subsequent studies; a finding that issuance of an order is *expected* to benefit the health of the population as a whole).

Furthermore, FDA must ensure that the advertising and labeling of the MRTTP enable the public to comprehend the information concerning modified risk and to understand the relative significance of such information in the context of total health and in relation to all of the tobacco-related diseases and health conditions (section 911(h)(1) of the FD&C Act).

After conducting a thorough scientific review of the information contained in the MRTTPAs; the recommendations from the Tobacco Products Scientific Advisory Committee; comments, data, and information submitted to FDA by interested persons; and other scientific information identified by the agency from other sources, I conclude that:

- With respect the exposure modification order request, the applicant **has demonstrated** that the products sold or distributed with the proposed modified risk information meet the standard under section 911(g)(2) of the FD&C Act, including that a measurable and substantial reduction in morbidity or mortality among individual tobacco users is reasonably likely in subsequent studies, and issuance of an order is expected to benefit the health of the population as a whole taking into account both users of tobacco products and persons who do not currently use tobacco products.

After conducting a thorough assessment of the scientific evidence, I find that “the IQOS system heats tobacco but does not burn it,” “this significantly reduces the production of harmful and potentially harmful chemicals,” and “scientific studies have shown that switching completely from conventional cigarettes to the IQOS system significantly reduces your body’s exposure to harmful or potentially harmful chemicals.” This determination is based on the substantial reduction across the constituents on FDA’s HPHC list, which demonstrates that, on the whole, as compared to combusted cigarette smoke, the process used to heat tobacco in the IQOS system significantly reduces the production of harmful and potentially harmful chemicals compared to cigarette smoke. The applicant also demonstrated that the magnitude of differences in biomarkers of exposure (BOEs) to 15 HPHCs when smokers switch completely to IQOS is substantial. The BOEs reduced reflect a range of chemical classes (e.g., carbonyls, aromatic amines, polycyclic aromatic hydrocarbons, nitrosamines) and toxicity classes (e.g., carcinogenic, cardiovascular, respiratory, reproductive). Although BOEs are not available for every constituent on the HPHC list, the comparative aerosol data provided demonstrate that many other HPHCs are significantly reduced compared to combusted cigarette smoke. It is reasonable to expect that completely switching to the IQOS system from combusted cigarettes would lower exposure to these constituents as well.

Although the non-clinical and clinical studies included in these applications were not sufficient to demonstrate that switching completely lowers the risk of disease compared to combusted cigarette

smoking and failed to meet the threshold for issuance of a risk modification order at this time, the totality of evidence presented suggests that a measurable and substantial reduction in morbidity or mortality among individual tobacco users is reasonably likely in subsequent studies. This determination predominantly stems from the substantial reduction in HPHCs relative to combusted cigarette smoke. Although some chemicals of potential concern (not on FDA's HPHC list) may be higher in IQOS users, the increase in these constituents does not impact the conclusion that the substantial reductions in HPHCs and findings from the toxicological evidence are reasonably likely to translate to lower risk of tobacco-related morbidity and mortality. The toxicological studies that indicated the potential for lower toxicity were based on the complete mixture of chemicals produced by the IQOS system, which would capture the impact of any increases in chemical concentrations relative to combusted cigarette smoke. In addition, when assessing the overall yield of chemicals on FDA's established list of HPHCs, along with chemicals of toxicological concern identified by the applicant not on FDA's HPHC list, the yields of potential carcinogens, respiratory toxicants, and reproductive/developmental toxicants were considerably lower in Heatstick aerosols compared with combusted cigarette smoke.

In terms of consumer understanding, the applications support the findings required for authorization. Actual consumer perception testing supports that consumer understanding is in line with the relative risks of the product that are reasonably likely. Importantly, consumers did not interpret the proposed claim to mean that the product causes no risk. After viewing product labels, labeling, and advertising with the reduced exposure claims, on average, consumers perceived IQOS as a product with moderate risks of a range of tobacco-related diseases and higher in risk than quitting smoking and using nicotine replacement therapy instead. After viewing product labels, labeling, and advertising with the reduced exposure claims, on average, consumers also perceived IQOS as a product that is lower in risk than cigarettes, although exposure to the claim did not appear to have a substantial impact on these perceptions. The novel design of the product may contribute to these risk perceptions in the same way that many consumers perceived that e-cigarettes were a less harmful alternative to cigarettes when their use was becoming more common.⁶ FDA considered whether these risk perceptions are problematic. As noted above, although the studies in the applications were not sufficient to support the issuance of a risk modification order at this time, the totality of the evidence supports that risk reduction is reasonably likely to be demonstrated in subsequent studies. In other words, consumer understanding is in line with the relative health risks of the product that are reasonably likely.

Under section 911(g)(2)(B)(iii), to issue an exposure modification order FDA must find that testing of actual consumer perception shows that, as the applicant proposes to label and market the product, consumers *will not be misled* into believing that the product *is or has been demonstrated* to be less harmful, or *is or has been demonstrated* to present less of a risk of disease than one or more other commercially marketed tobacco products. FDA interprets this to mean finding that consumers do not hold inaccurate beliefs or are not misled regarding the definitiveness of the evidence regarding the relative risks or harm of the product. As noted above, testing of actual consumer perception showed that consumer understanding is in line with the relative health risks of the product that are reasonably likely and the current state of the evidence.

FDA considered whether including a disclaimer on product labeling and advertising would improve consumer understanding (e.g., improve understanding that although risk reduction is reasonably likely, it has not yet been demonstrated in scientific studies). Specifically, as part of its consumer perception

⁶ Pepper JK, Brewer NT. Electronic nicotine delivery system (electronic cigarette) awareness, use, reactions and beliefs: a systematic review. *Tob Control*. 2014 Sep;23(5):375-84.

study, the applicant tested the impact of a disclaimer (as part of its “PMI warning”) that states, “It has not been demonstrated that switching to the IQOS system reduces the risk of developing tobacco-related diseases compared to smoking conventional cigarettes.” However, as described in the body of the review, the study design limited the inferences that can be drawn from the study findings. Moreover, the currently available evidence suggests that, in general, disclaimers on tobacco products are often limited in their effectiveness.^{7,8,9} Accordingly, I do not expect that the disclaimer would improve consumer understanding. As noted above, testing of actual consumer perception shows that as the applicant proposes to label and market the product (without a disclaimer), consumers will not be misled about the current state of the evidence regarding the relative health risks of the product. Overall, the available evidence demonstrates that consumers generally understand the relative health risks of the product that are reasonably likely, which would be expected to impact behavior in a way that promotes public health.

One consumer misperception uncovered by the applicant’s studies was the perception that IQOS is less addictive than combusted cigarettes. To address this, FDA’s marketing authorization order for the IQOS system (PM0000424-PM0000426, PM0000479) requires inclusion of the warning statement “WARNING: This product contains nicotine. Nicotine is an addictive chemical.” on the package labels of all Heatsticks packs and on all kits containing Heatsticks packs as well as in all advertisements for such products and kits. In addition, the applicant did not assess what smokers understand about the health effects of *partially* switching from combusted cigarettes to IQOS, which would not be expected to result in the benefits of exposure reduction. As described below, postmarket surveillance should assess the extent to which consumers continue to understand the proposed modified risk information, including that the benefits of reducing exposure to harmful and potentially harmful chemicals require complete cessation of combusted cigarette smoking.

The available scientific evidence demonstrates that the issuance of an exposure modification order for IQOS would be appropriate to promote the public health and is expected to benefit the health of the population as a whole, taking into account both users of tobacco products and persons who do not currently use tobacco products. After viewing labels, labeling and advertising (LLA) materials with the exposure reduction claim, many smokers expressed high interest in IQOS and intended to use it. Although some former smokers expressed interest in IQOS, the addition of the claim did not appear to increase interest among this group. In addition, very few never smokers expressed interest in IQOS or intended to use it. Although dual use of IQOS and combustible cigarettes was commonly observed across the behavioral studies submitted, this was in the absence of clear information that complete switching is necessary to achieve the benefits of the product. The proposed MRTP claim informs consumers that complete switching from cigarettes to IQOS significantly reduces exposure to HPHCs. Finally, the currently available evidence suggests that youth uptake of IQOS is currently low in countries where it has been measured. However, given that IQOS is still a relatively new product, the uptake and use patterns among youth in these markets, or any other market that may start selling IQOS, is unclear. Given that youth are at increased risk, generally, for initiating tobacco use and the uncertainty around the effect of modified risk information on youth use, it is critical that any marketing plans be designed to prioritize preventing youth exposure. FDA’s marketing authorization order for the IQOS system

⁷ Baig SA, Byron MJ, Lazard AJ, Brewer NT. "Organic," "natural," and "additive-free" cigarettes: comparing the effects of advertising claims and disclaimers on perceptions of harm. *Nicotine Tob Res.* 2019;21(7):933-939.

⁸ Byron MJ, Baig SA, Moracco KE, Brewer NT. Adolescents' and adults' perceptions of 'natural', 'organic' and 'additive-free' cigarettes, and the required disclaimers. *Tob Control.* 2016;25(5):517-520.

⁹ O'Connor RJ, Lewis MJ, Adkison SE, Bansal-Travers M, Cummings KM. Perceptions of "natural" and "additive-free" cigarettes and intentions to purchase. *Health Educ Behav.* 2017;44(2):222-226.

(PM0000424-PM0000426, PM0000479) includes postmarket requirements to help ensure that youth exposure to tobacco marketing is being minimized. This includes informing FDA of all advertising and marketing plans prior to dissemination, implementing plans to restrict youth access and limit youth exposure to the products' labeling, advertising, marketing, and/or promotion, and requiring the applicant to track and measure actual delivery of all advertising impressions, including among youth. In addition, as described below, postmarket surveillance and studies should be conducted to monitor youth awareness and use of the IQOS system to ensure that marketing of the products as MRTPs will not have the unintended consequence of leading to increased use of these products among youth.

Section 911(g)(2)(C)(i) of the FD&C Act provides that an MRTP exposure modification order shall be limited for a term of not more than 5 years. I recommend authorization for a period of 4 years, given that these would be the first MRTP authorizations issued by the Agency for a novel tobacco product. The IQOS system has only been on the U.S. market for a limited period of time and has only been marketed internationally for a few years. The greater uncertainty associated with such a novel product warrants additional caution. Although this review has found that an exposure modification order for the products would be appropriate to promote the public health and is expected to benefit the health of the population as a whole, that determination may change over time as a function of how the products are actually used by consumers. Therefore, monitoring use of the IQOS system with Heatsticks in terms of uptake, dual use, and complete switching should be required, including the potential for initiation among youth. As described below, postmarket surveillance and studies must include an assessment of MRTP users' behavior and understanding over time. A 4-year period is a reasonable amount of time to assess whether there is appropriate consumer understanding and to generate preliminary data on behavior in postmarket surveillance and studies to assess whether the standard continues to be met and whether the order should be renewed.

II. Regulatory Information

A. Regulatory History

On November 18, 2016, Philip Morris Products (PMP) S.A. submitted modified risk tobacco product applications (MRTPAs) for the IQOS system, including the Holder and Charger and three types of Heatsticks: Marlboro Heatsticks, Marlboro Smooth Menthol Heatsticks, and Marlboro Fresh Menthol Heatsticks, which were received by FDA on December 5, 2016.

FDA received the following amendments to the IQOS applications:

- January 25, 2017, containing clarification of product configurations, modified risk claims, and warnings
- February 8, 2017, containing clarification of product configurations
- March 16, 2017, containing response to the Advice/Information (AI) Request letter issued March 2, 2017
- March 20, 2017, containing response to the Advice/Information (AI) Request letter issued March 2, 2017
- May 10, 2017, containing re-submitted data previously provided in the March 16, 2017 amendment, with additional study reports and data
- June 8, 2017, containing manufacturing site details

- June 21, 2017, containing a letter of authorization for a tobacco product master file and re-submitted images for the IQOS device package
- June 30, 2017, containing revised manufacturing schedules
- August 10, 2017, containing confirmation of manufacturing facility inspection dates
- August 31, 2017, containing a request for additional time to respond to the AI Request letter issued August 4, 2017, and confirmation that battery samples were sent to the Winchester Engineering Analytical Center
- August 31, 2017, containing clarification of activities at (b) (4)
- September 11, 2017, containing responses to the AI Request letter issued August 4, 2017
- September 13, 2017, containing responses to the AI Request letter issued August 4, 2017
- November 1, 2017, containing withdrawal of certain case report forms and certain raw data files
- November 16, 2017, containing additional information for response to the AI Request letter issued August 4, 2017
- December 8, 2017, containing additional information in response to the AI Request letter issued August 4, 2017, and data from recently completed studies
- December 22, 2017, containing the response to the IQOS PMTA AI Request letter issued November 22, 2017
- December 26, 2017, containing additional information in response to the AI Request letter issued November 22, 2017
- January 24, 2018, containing two re-submitted figures (#1 and 4) with missing words that were submitted in the amendment submitted September 13, 2017
- February 2, 2018, containing clarification of the ongoing “P1 Characterization” study
- February 26, 2018, containing toxicological study update
- February 28, 2018, containing clinical study update
- March 29, 2018, containing a response to the AI Request letter issued March 2, 2018 for environmental science questions
- April 26, 2018, containing the P1 Characterization study update
- May 16, 2018, containing a Safety Update Report (SUR) in accordance with ICH for the period January 1, 2017 – December 31, 2017
- May 23, 2018, containing a response to the AI Request letter issued April 23, 2018 for chemistry and toxicological questions
- June 11, 2018, containing data for the completed clinical study ZRHR-ERS-09-US
- June 13, 2018, containing responses to clarifying questions about PMP S.A.’s SUR submitted May 16, 2018
- August 3, 2018, containing responses to clarifying questions about PMP S.A.’s SUR submitted May 16, 2018
- August 31, 2018, containing response to information request email on July 27, 2018 for a tabulated index of the scientific references in Module 9
- September 4, 2018, containing results of the finalized in vivo 18-month combined chronic toxicity and carcinogenicity study in A/J mice
- September 25, 2018, containing additional information for clinical study ZRHM-PK-06-US and HPHC analysis
- October 23, 2018, containing amended versions of two preclinical study reports submitted in the September 4, 2018 amendment
- December 20, 2019, containing a response to November 20, 2019 teleconference request for carcinogenicity study summary report

Under section 910 of the FD&C Act, the applicant requested authorization to market the IQOS system with Marlboro Heatsticks, Marlboro Smooth Menthol Heatsticks, and Marlboro Fresh Menthol Heatsticks without modified risk claims. FDA authorized the marketing of the IQOS system without modified risk claims on April 30, 2019. The technical project lead (TPL) review for the accompanying premarket tobacco product applications (PMTAs) provides detail on the engineering, chemistry, stability, and manufacturing of the products, including the results of FDA inspections of manufacturing sites, and is available at: <https://www.fda.gov/tobacco-products/premarket-tobacco-product-applications/premarket-tobacco-product-marketing-orders>. Where relevant, the present review reflects determinations made in the PMTA TPL review.

The focus of this review of the MRTPAs is on the (1) assessment of the proposed modified risk claims, (2) relative health risks of the products, (3) consumer understanding, and (4) potential impact to the population from marketing the products with the proposed modified risk information.

B. Proposed Modified Risk Tobacco Product

1. Description of Product

The applicant describes the IQOS Tobacco Heating System (THS) as a “heat-not-burn tobacco product,” consisting of three main components (Figure 1):

- **IQOS Heatstick:** The Heatstick contains a tobacco plug consisting of crimped cast tobacco sheet made from ground tobacco powder. It is designed to function with the IQOS holder to produce an aerosol when the plug is heated. It is a filtered non-combusted cigarette.
- **IQOS Holder:** The Heatstick is inserted into the Holder, which heats the tobacco material by means of an electronically controlled heating blade. The Holder is activated by the user by pressing the activation button for a set period until the Holder light begins to blink, signaling that the product may be used. The Holder is designed to function for a maximum of six minutes or 14 puffs, whichever comes first, after which it must be recharged and a new Heatstick must be inserted.
- **IQOS Charger:** The Charger is used to recharge the Holder after each use. The Charger stores sufficient energy for the use of approximately 20 Heatsticks and can be recharged from household power.



Figure 1. Components of IQOS Tobacco Heating System

(Source: MRTPAs section 2.7)

The applicant uses different terms to describe the products tested in the studies presented in the applications. In a March 2017 amendment to the applications, the applicant stated that THS 2.2 is the investigational product name for the product it plans to market as the IQOS system. This review predominantly refers to the product by its commercial name, the IQOS system. However, the terms THS, THS 2.2, and IQOS should be considered synonymous for the purpose of this review.

2. Proposed Modified Risk Claims

PMP S.A. requested MRTP orders under sections 911(g)(1) and 911(g)(2) of the Federal Food, Drug, and Cosmetic Act (FD&C Act).

Risk Modification Order Request Under 911(g)(1):**Modified Risk Claim #1:**

“AVAILABLE EVIDENCE TO DATE:

- The IQOS system heats tobacco but does not burn it.
- This significantly reduces the production of harmful and potentially harmful chemicals.
- Scientific studies have shown that switching completely from conventional cigarettes to the IQOS system can reduce the risks of tobacco-related diseases.”¹⁰

Modified Risk Claim #2:

“AVAILABLE EVIDENCE TO DATE:

- Switching completely to IQOS presents less risk of harm than continuing to smoke cigarettes.”

Exposure Modification Order Request Under 911(g)(2):**Modified Risk Claim #3:**

“AVAILABLE EVIDENCE TO DATE:

- The IQOS system heats tobacco but does not burn it.
- This significantly reduces the production of harmful and potentially harmful chemicals.
- Scientific studies have shown that switching completely from conventional cigarettes to the IQOS system significantly reduces your body’s exposure to harmful or potentially harmful chemicals.”

In its MRTPAs, the applicant proposed to use the Surgeon General’s (SG) Warnings currently required for cigarettes. FDA’s PMTA authorization for these products (FDA, 2019a) required the removal of the SG Warning stating, “SURGEON GENERAL’S WARNING: Cigarette Smoke Contains Carbon Monoxide,” and also required that the products’ labeling and advertising include the following warning: “WARNING: This product contains nicotine. Nicotine is an addictive chemical.” In its MRTPAs, the applicant also evaluated alternate versions of labeling and advertising materials that contained what it called “PMI Warnings,” additional text that varied based on modified risk claim. The applicant did not ultimately request to use these PMI warnings instead of the SG warnings as part of its MRTPAs, but since the PMI warnings were included in the applicant’s consumer perception studies and contain information potentially relevant to consumer perception and understanding information, they were examined in the social science review and are considered here, as applicable.

More information about how PMP S.A. proposes to communicate the proposed modified risk claims, along with findings from its consumer perception studies assessing the impact of these claims and warnings, is described in section III.B.

C. Tobacco Products Scientific Advisory Committee (TPSAC)

Pursuant to section 911(f) of the FD&C Act, FDA referred the MRTPAs to TPSAC, and TPSAC reported its recommendations on the applications during an open public committee meeting held on January 24-25, 2018. At the meeting, the committee discussed the MRTPAs, including the adequacy of the scientific

¹⁰ There were slight variations in the wording of the proposed claims in different parts of the applications. The claims listed here reflect the specific language that was tested by the applicant and presented in sample labeling in the applications.

evidence to support the proposed modified risk marketing. Information about the meeting, including the complete transcript, is available at:

<https://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/TobaccoProductsScientificAdvisoryCommittee/ucm583080.htm>

FDA shared its preliminary assessment of the applications with the committee, focusing on the scientific accuracy of the proposed modified risk claims, product use behavior, and consumer understanding and perceptions of the proposed modified risk claims. TPSAC was asked to discuss FDA's preliminary assessment, including 1) whether the applicant had demonstrated that each of the proposed modified risk claims was scientifically accurate; 2) if they found the reduced exposure claim to be accurate, whether the applicant had demonstrated it was reasonably likely the reductions in exposure would translate to a measurable and substantial reduction in morbidity and/or mortality; 3) the likelihood that existing combusted cigarette smokers would initiate use of the IQOS system, completely switch to IQOS, and/or become long-term dual users of IQOS and combusted cigarettes; 4) the likelihood that non-users, including youth and former smokers, would use IQOS; and 5) consumer understanding and perceptions of the proposed modified risk claims. A summary of TPSAC's discussions and votes on these topics is presented below. FDA's assessment of these discussions and votes is included in section III of this review, as well as in individual discipline reviews.

TPSAC members were asked to discuss the evidence related to the health risks of the IQOS system and the scientific accuracy of proposed modified risk claims. Committee members began by discussing and voting on the scientific accuracy of the reduced risk claims. When asked whether the applicant had demonstrated that "Scientific studies have shown that switching completely from cigarettes to the IQOS system can reduce the risks of tobacco-related diseases," 8 of the 9 voting members voted "no" and one member abstained. While several members noted that they thought the evidence suggested there was the potential for reduced risk of disease, most members stated that the lack of long-term human studies led them to conclude that a reduction in risk of tobacco-related diseases had not been demonstrated. When asked to discuss and vote on the scientific accuracy of the other reduced risk claim, "Switching completely to IQOS presents less risk of harm than continuing to smoke cigarettes," 4 of the voting members found it to be scientifically supportable and 5 did not. TPSAC members indicated more comfort with the word "harm" relative to the term "tobacco-related diseases," and this seemed to account for the increased support for the latter statement relative to the former.

Committee members were then asked to discuss and vote on the evidence related to exposure to chemicals, specifically whether the applicant had demonstrated that the reduced exposure claim "Scientific studies have shown that switching completely from cigarettes to the IQOS system significantly reduces your body's exposure to harmful or potentially harmful chemicals" is true. Among the 9 voting members, 8 members voted "yes" and 1 voted "no". Those members who voted that the reduced exposure statement was true were then asked whether the applicant had demonstrated that these reductions in exposure are reasonably likely to translate to a measurable and substantial reduction in morbidity and/or mortality. Two voted "yes", 5 voted "no", and 1 abstained. Those who voted yes said they did so assuming that such a large reduction in exposure would likely result in reduction in disease, even if that had not been demonstrated in the short-term studies submitted by the applicant. Those members who voted "no" stated they did not believe the applicant *demonstrated* that a translation to substantial reduction in morbidity and/or mortality was likely. See section III.A for my assessment of this discussion.

TPSAC was also asked to discuss the evidence regarding the likelihood that existing combusted cigarette smokers will initiate use of the IQOS system, completely switch to IQOS, and/or become long-term dual

users of IQOS and combusted cigarettes. Voting members were asked to indicate whether the likelihood was low, medium, or high. When asked to indicate the likelihood that existing combusted cigarette smokers would completely switch to IQOS, 7 voting members stated “low” and 2 members stated “medium”. When asked about the likelihood of dual use of combusted cigarettes and IQOS, 1 voting member stated “low”, 5 stated “medium”, and 3 stated “high”. Among those who reported a medium or high likelihood of dual use, there was discussion of patterns of use being similar to those seen among e-cigarette users, where there is significant dual use of e-cigarettes and combusted cigarettes by some users.

When committee members were asked to vote on the likelihood that never smokers, particularly youth, will become established users of the IQOS system, 4 voted “low”, 1 voted “medium”, 2 voted “high”, and 2 abstained. Those who thought there was a medium or high likelihood of never smokers becoming established users of IQOS cited the e-cigarette experience as the basis for their decision, with concern that the product and/or marketing may be appealing to youth. Those members who voted “low” thought there would be low uptake of IQOS overall, including among youth. Although the questions were framed in the context of the MRTPAs, the discussion focused more on the product itself, rather than the product marketing with modified risk claims. See section III.C for my assessment of this discussion.

Finally, TPSAC was asked to discuss the evidence regarding consumer understanding and perceptions of the proposed modified risk claims and whether the applicant had demonstrated that consumers accurately understood the risks of IQOS use as conveyed by the modified risk information. Voting members unanimously voted “no”. Although the discussion around the rationale informing each vote was minimal, one member stated the applicant had not demonstrated an *increase* in consumer understanding of the risks. Others expressed concern about the complexity of the message. Several members also expressed concern about the lack of evidence that consumers understood that complete switching was necessary to achieve the purported benefits communicated in the modified risk claims. There was also discussion of the need to ensure that the risk of addiction was clearly communicated. See section III.B for my assessment of this discussion.

D. Public Availability of MRTPAs

Pursuant to section 911(e) of the FD&C Act, FDA made PMP S.A.’s MRTPAs available to the public (except matters in the applications that are trade secrets or are otherwise confidential, commercial information). The docket for public comment on the MRTPAs for PMP S.A.’s IQOS system with Marlboro Heatsticks was open from June 15, 2017 to February 11, 2019 and then was reopened between January 24 and February 24, 2020. FDA received 256 unique public comments from individuals, academia, health professionals, state and local governments, and other organizations. In addition to legal and advocacy issues, the comments included independent nonclinical, clinical, and consumer perception studies, critiques of the applicant’s studies and interpretation of findings, concerns about potential appeal to youth, and concerns about marketing and advertising strategies used by PMP S.A. in countries where IQOS is currently sold. Comments also included articles from *Tobacco Control* (Volume 27, Supplement 1) published in November 2018. The supplement contained commentaries, research papers, and brief reports on heated tobacco products, including IQOS. Many of the issues and concerns raised in the public comments were also identified during FDA’s scientific review of the applications. FDA considered all significant comments when making the final determination.

III. Summary of Scientific Evidence

The applicant argues that the IQOS system with Heatsticks represents a less harmful alternative for current cigarette smokers by providing evidence that the product design involves heating tobacco, rather than burning it; aerosol testing in comparison to combusted cigarette smoke; toxicological evidence from in vitro and in vivo studies; and clinical studies assessing biomarkers of exposure and potential harm in smokers who switch from combusted cigarettes to the IQOS system. This section assesses the evidence on the relative health risks to individual users, including assessment of the scientific accuracy of the modified risk information proposed to be communicated by the applicant to consumers. Subsequent sections of the review address consumer understanding and perceptions of the proposed modified risk information and its potential impact on the population as a whole, including both current users and non-users of tobacco.

A. Relative Health Risks of the Proposed MRTPs to Individual Tobacco Users

1. Combustion

The applicant's argument that the IQOS system with Heatsticks will reduce exposure and disease risk starts with its assertion that the product is designed to heat tobacco, but not burn it. The applicant provided several lines of evidence to support this claim. First, the heating blade is electronically controlled to heat to a maximum temperature of 350°C during product use. The applicant provided detailed information on the verification of heating blade temperature and quantitative thermal analysis using infrared thermography, demonstrating that the temperature does not exceed 350°C. The combustion of combusted cigarettes typically occurs between 470–812°C, which is well above the maximum temperature of the IQOS system. The exception is during the cleaning process, in which the blade is heated to a higher temperature to facilitate the removal of deposits left after multiple uses. The cleaning process, however, can only be initiated while the Holder is stored within the Charger and there is no Heatstick inserted.

Another characteristic of combustion is it is an exothermic reaction in which heat is released. The applicant provided a report titled "Analysis of EHTP Features with respect to Biomass/Tobacco Combustion" (see Appendix A.2.1-1 of the MRTPAs) which demonstrates that the temperature is lower during puffing than between puffing intervals in the IQOS system with Heatsticks (~ 40°C lower). In contrast, the temperature of combusted cigarettes is higher during puffing (~ 900°C) than between puffing intervals (~ 400°C). During puffing of a combusted cigarette, air, including oxygen, is drawn through the filter of a cigarette at the mouth-end and the temperature of the tobacco increases. In contrast, the temperature of the tobacco decreases during puffing in the IQOS system with Heatsticks, indicating that the process is not exothermic.

Combustion is an exothermic chemical process that requires the presence of oxygen. The applicant assessed the formation of 30 HPHCs in nitrogen and oxygen environments. If combustion occurred, we would expect the levels of these HPHCs to be higher in the oxygen environment compared to the levels of HPHCs in the absence of oxygen. The applicant compared the levels of 30 HPHCs, including carbon monoxide (CO), nitrogen oxides, benzo[a]pyrene, formaldehyde, and acrolein, in a nitrogen atmosphere, synthetic air, and International Organization for Standardization (ISO) standard "ambient air." The levels of the 30 HPHCs were very similar in a nitrogen atmosphere, in synthetic air, and in ISO standard "ambient air", suggesting that these 30 HPHCs are not formed in the presence of oxygen, unlike

compounds produced by combustion. In addition, CO is present in IQOS aerosol at substantially lower levels than cigarette smoke. It is still present at minimal levels because CO can also be formed by thermal decomposition (pyrolysis) of tobacco constituents.

Finally, the level of nitrogen oxides produced by the IQOS system is an additional indicator to assess the presence of combustion. Nitric oxide is formed in combusted cigarettes at two temperature ranges. At 275–375°C, the amount of nitric oxide produced correlates to the amount of nitrate present in tobacco. Nitric oxide formed at 275–375°C is independent of the concentration of oxygen, suggesting the absence of combustion. At 425–525°C, nitric oxide originates from the oxidation of nitrogen in the tobacco char.¹¹ The applicant measured the level of nitrogen oxides in the aerosol of the IQOS system with Heatsticks, which resulted in 6% higher nitrogen oxides in a nitrogen atmosphere compared to synthetic air and 37% higher nitrogen oxides compared to ISO standard ambient air. The low level of nitrogen oxides (~13 µg/Heatstick) and the small differences in the level of nitrogen oxides between the nitrogen atmosphere and synthetic air suggest that the nitrogen oxides are formed mainly by nitrate decomposition and not by combustion.

In the published literature, Davis et al.¹² concluded that the IQOS system is not strictly a “heat-not-burn” tobacco product because the tobacco appears to char without ignition. However, the presence of charring in the Heatsticks does not necessarily imply that the product burns tobacco because the charring could be produced by pyrolysis.

Conclusion

The low temperature in the IQOS system ($\leq 350^{\circ}\text{C}$), the lack of an exothermic process, the similar levels of HPHCs in the presence and absence of oxygen, and the low level of nitrogen oxides in the aerosol of the IQOS system with Heatsticks suggest that combustion does not occur in the IQOS system with Heatsticks when it is used as intended. **There is sufficient evidence to support the following statement: *The IQOS system heats tobacco but does not burn it.***

2. Harmful and Potentially Harmful Constituents (HPHCs)

This section presents the applicant’s HPHC testing data, including a comparison of the concentrations of compounds on FDA’s HPHC list between the aerosol of the IQOS system and smoke from combusted cigarettes. In addition, the applicant identified the presence of non-HPHCs found at higher levels in the aerosol of the IQOS system. The applicant’s findings are presented along with findings from FDA’s Southeast Tobacco Laboratory (STL) and the published literature.

The applicant submitted HPHC testing data for the IQOS system with different Heatstick variants from several different studies. A description of these studies is shown in Table 1. A detailed evaluation of the methods of these studies can be found in the Chemistry review.

¹¹ Im H, Rasouli F, Hajaligol M. Formation of nitric oxide during tobacco oxidation. *J Agric Food Chem*. 2003;51(25):7366-7372.

¹² Davis B, Williams M, Talbot P. IQOS: evidence of pyrolysis and release of toxicants from plastic. *Tob Control*. 2019 Jan;28(1):34-41.

Table 1. Chemical testing reported by the applicant to characterize constituent levels in the IQOS System with Marlboro Heatsticks

Study	Description
TNCO	Tar, nicotine, and carbon monoxide were measured in the three Heatstick variants using the ISO regimen methods.
FDA 18+6 Study	18 HPHCs were measured using ISO and modified Health Canada Intense regimens and 6 HPHCs were measured in tobacco filler in the three Heatstick variants.
PMI-58 Study	Glycerol, nicotine, tar, total particulate matter (TPM), water and 54 HPHCs were measured using a modified Health Canada Intense smoking regimen in the three Heatstick variants and compared against the 3R4F reference cigarette and mainstream cigarette smoke from 31 Philip Morris USA marketed cigarettes.
93-FDA-HPHCs Study	Tar, TPM, water, 108 HPHCs ¹³ , and 13 compounds not included in the FDA-93 HPHCs list in the aerosol of the IQOS system with two Heatstick variants (MR0000059 and MR0000060) using modified Health Canada Intense smoking regimen. Comparison is performed against the 3R4F reference cigarette.
Non-Targeted Differential Screening	Constituents present in the aerosol of the IQOS system with the three Heatstick variants at higher concentrations than the mainstream smoke of the 3R4F reference cigarette using modified Health Canada Intense smoking regimen.
P1 Characterization	Chemical constituents present at concentrations higher than 100 ng per Heatstick in the aerosol of MR0000059 using the modified Health Canada Intense smoking regimen.

IQOS Compared to Combusted Cigarettes

Across the three Heatstick variants, except for nicotine and anabasine, the HPHC levels were 47-99.9% lower in the aerosol of the Heatsticks compared to the mainstream smoke of the 3R4F reference cigarette, per unit. When normalized by nicotine concentration, this translated to 20-99.8% lower concentrations in the aerosol produced by the Heatsticks (PMI-58 study and 93-FDA-HPHCs study). Across the Heatstick variants, anabasine was 13-17% lower, but when normalized by nicotine concentration was 26-33% higher than the mainstream smoke of the 3R4F reference cigarette (93-FDA-HPHCs study). The HPHC levels were 60-99.9% lower in the aerosol produced by the Heatsticks compared to the mainstream smoke of the mean of 31 U.S. market cigarettes selected by the applicant per unit base. The HPHC levels were 39-99.8% lower in the aerosol produced by the Heatsticks when normalized by nicotine concentration (PMI-58 study). Among the 108 HPHCs reported in the FDA-93 HPHCs study, 41 HPHCs were below the limit of quantification (LOQ) in both the aerosol of the IQOS system with Heatsticks and the mainstream smoke from the 3R4F reference cigarette. Sixty-six HPHCs were lower in the aerosol of the IQOS system with Heatsticks compared to the mainstream smoke of the 3R4F reference cigarette, per unit. When normalized by nicotine concentration, only anabasine was higher in the aerosol of the IQOS system with Heatsticks.

Nicotine: Across the three Heatstick variants, nicotine was found to be 26-42% lower in the aerosol of the IQOS system with Heatsticks compared to the mainstream smoke of 3R4F reference cigarette and the mean of the U.S. market cigarettes per unit. This is consistent with Farsalinos et al., who found that

¹³ FDA's established list of 93 HPHCs includes the category of "cresols (o-, m-, and p-cresol)" and "chlorinated dioxins/furans". The 108 HPHCs in this study included 3 cresols and 17 chlorinated dioxins/furans, so 90 of the compounds or classes on the FDA HPHC list were tested. There were 3 HPHCs on FDA's list that were not tested in this study. The applicant stated that coumarin, NSAR, and Alfatoxin B1 were not analyzed because these HPHCs are found primarily in smokeless tobacco and not in tobacco smoke.

the concentration of nicotine per gram of tobacco in the Heatsticks is similar to the concentration in combusted cigarettes, and the IQOS system delivers less nicotine in the aerosol per Heatstick compared to combusted cigarettes.¹⁴

Total Particulate Matter (TPM): TPM was 20-32% higher in the aerosol of the IQOS system with Heatsticks compared to mainstream smoke in combusted cigarettes, per unit. In the three Heatstick products, the level of tar reported by the applicant (defined as total weight of solid and liquid residue in cigarette smoke after the weight of nicotine and water has been subtracted) was 20-36% lower in the aerosol of the IQOS system with Heatsticks compared to the 3R4F reference cigarette, per unit. The level of tar is consistent with the data reported by Li et al.¹⁵ and Bekki et al.¹⁶ However, Mallock et al.¹⁷ reported higher levels of tar in the IQOS system with Heatsticks (21-33%) compared to the 3R4F reference cigarette. It is important to note that the composition of the TPM produced by the IQOS system with Heatsticks is different from the TPM in the 3R4F reference cigarette. The TPM formed in the aerosol contains 14% particulate matter (solid), 76% water, and 10% glycerol. The TPM formed in mainstream cigarette smoke contains 63% particulate matter (solid), 32% water and 5% glycerol.¹⁸ Because HPHCs are found in the solid particulate matter, it is expected that HPHC yields would be higher in cigarette smoke than in aerosol.

Volatile Gases, Polycyclic Aromatic Hydrocarbons (PAHs), Volatile Organic Compounds (VOCs): Since the IQOS system heats tobacco at a temperature lower than 350°C, it is expected that the levels of compounds formed by combustion would be substantially lower than combusted cigarettes. These compounds include volatile gases such as carbon monoxide and nitrogen oxides; PAHs such as benzo[a]pyrene, and VOCs such as toluene, acetaldehyde, and hydrogen cyanide.¹⁹ In the data provided by the applicant, these compounds were all reduced substantially when compared to 3R4F reference cigarette smoke.

Acrolein and Formaldehyde: Other HPHCs might be expected to be impacted by the design and use of the IQOS system with Heatsticks. For example, acrolein is produced by dehydration of glycerol and formaldehyde is produced by thermal degradation of glycerol and propylene glycol.²⁰ However, despite the higher levels of glycerol and propylene glycol in the IQOS system, the levels of acrolein and formaldehyde in the aerosol of the Heatsticks were substantially lower than mainstream cigarette smoke (89-95% lower for acrolein and 66-91% lower for formaldehyde). This is likely due to the lower temperature in the IQOS system (<350°C) compared to the temperature of combusted cigarettes.

¹⁴ Farsalinos K, Yannovits N, Sarri T, Voudris V, Poulas K. Nicotine delivery to the aerosol of a heat-not-burn tobacco product: comparison with a tobacco cigarette and e-cigarettes. *Nicotine Tob Res.* 2018 Jul 9;20(8) 1004-1009.

¹⁵ Li X, Luo Y, Jiang X, et al. Chemical analysis and simulated pyrolysis of tobacco heating system 2.2 compared to conventional cigarettes. *Nicotine Tob Res.* 2019 Jan 1;21(1):111-118.

¹⁶ Bekki K, Inaba Y, Uchiyama S, Kunugita N. (2017). Comparison of chemicals in mainstream smoke in heat-not-burn tobacco and combustion cigarettes. *J UOEH.* 2017;39(3):201-207.

¹⁷ Mallock N, Böss L, Burk R, et al. Levels of selected analytes in the emissions of “heat not burn” tobacco products that are relevant to assess human health risks. *Arch Toxicol.* 2018;92(6):2145-2149.

¹⁸ Schaller JP, Keller D, Poget L, et al. Evaluation of the Tobacco Heating System 2.2. Part 2: Chemical composition, genotoxicity, cytotoxicity, and physical properties of the aerosol. *Regul Toxicol Pharmacol.* 2016 Nov 30;81 Suppl 2:S27-S47.

¹⁹ Centers for Disease Control and Prevention (CDC). *Chemistry and Toxicology of Cigarette Smoke and Biomarkers of Exposure and Harm in How Tobacco Smoke Causes Disease: The Biology and Behavioral Basis for Smoking-Attributable Disease: A Report of the Surgeon General.* Atlanta, GA: CDC; 2010.

²⁰ Sleiman M, Logue J, Montesinos V, et al. Emissions from electronic cigarettes: key parameters affecting the release of harmful chemicals. *Environ Sci Technol.* 2016;50:9644-9651.

Ammonia and Acrylamide: Ammonia and acrylamide were 58-66% lower in the aerosol of the IQOS system with Heatsticks compared to mainstream cigarette smoke. While there are lower levels of ammonia and acrylamide in the aerosol of the IQOS system with Heatsticks, it is not as significant as the reduction observed for other HPHCs, such as carbon monoxide. Ammonia and acrylamide can be formed through the pyrolysis of amino acids at temperatures of 180-210°C.^{21,22} Both ammonia and acrylamide could be formed at the temperature of operation of the IQOS system.

N-nitrosornicotine (NNN) and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK): The tobacco in Heatsticks is composed of a higher proportion of reconstituted tobacco than the 3R4F reference cigarette and other combusted cigarettes and studies have shown that the mainstream smoke of burley and reconstituted tobaccos contain much higher tobacco-specific nitrosamine (TSNA) levels than bright and oriental tobacco.²³ However, NNN and NNK were found to be 92-98% lower in the aerosol of the Heatsticks compared to cigarette smoke. NNN and NNK are formed by nitrosation of alkaloids present in the tobacco plant during tobacco processing, curing, and storage. PMP S.A. scientists studied the influence of tobacco blends on the formation of HPHCs in the IQOS system with Heatsticks and stated that, "Selecting tobaccos with low concentrations of TSNA should reduce exposure to these HPHCs." While NNN and NNK levels are lower in the aerosol of the IQOS system with Heatsticks due to heating of tobacco at temperatures less than 350°C, lower aerosol levels are likely also caused by selecting tobacco blends with lower propensity for TSNA formation and limiting the use of nitrogen fertilizer.²⁴

Other Constituents in IQOS

In the non-targeted differential screening study, the applicant identified 53-61 compounds across Heatstick variants (80 unique compounds) that are either present exclusively or are found in higher quantities in the aerosol of the IQOS system with Heatsticks compared to the mainstream smoke in the 3R4F reference cigarette. These compounds include menthol-related constituents, alkaloids, and flavors. Among the constituents with the greatest increases relative to cigarettes were 1,4-dioxane, 2-ethyl-5-methyl, propylene glycol, glycidol, and acetol. In the P1 characterization study, the applicant reported 498 compounds, except for water, nicotine, and glycerol, present in the aerosol of MR0000059 at a concentration higher or equal to 100 ng/Heatstick. All the compounds were also identified in the mainstream smoke of the 3R4F reference cigarette.

The applicant included a limited toxicological evaluation of the eighty chemicals found exclusively in Heatstick aerosols or at higher concentrations than in the 3R4F reference cigarette. In total, the applicant reported four possible or probable human carcinogens, nineteen other chemicals that generated structural alerts in the Organisation for Economic Co-operation and Development (OECD) quantitative structure-activity relationship (QSAR) toolbox, and nine additional chemicals identified in the applicant's literature review as being of toxicological concern. Each of these chemicals was reported at higher concentrations in the aerosol of the IQOS system with Heatsticks compared to 3R4F reference cigarette smoke.

²¹ Moldoveanu S. *Pyrolysis of Organic Molecules: Applications to Health and Environmental Issues*. New York, NY: Elsevier Science; 2010.

²² Stadler R, Blank I, Varga N, et al. (2002). Food chemistry: acrylamide from Maillard reaction products. *Nature*. 2002;419:449-450.

²³ Ding YS, Zhang L, Jain RB, et al. Levels of tobacco-specific nitrosamines and polycyclic aromatic hydrocarbons in mainstream smoke from different tobacco varieties. *Cancer Epidemiol Biomarkers Prev*. 2008;17(12):3366-3371.

²⁴ Centers for Disease Control and Prevention (CDC). *Chemistry and Toxicology of Cigarette Smoke and Biomarkers of Exposure and Harm in How Tobacco Smoke Causes Disease: The Biology and Behavioral Basis for Smoking-Attributable Disease: A Report of the Surgeon General*. Atlanta, GA: CDC; 2010.

In order to assess the significance of this increase in constituents, the toxicological reviewer conducted comparisons of the total concentration of carcinogens, respiratory toxicants, and reproductive or developmental toxicants between Heatstick aerosols and the smoke of reference cigarette 3R4F. Overall, the concentration of these established and potential carcinogens was reduced by approximately 82% in the Heatstick aerosol relative to the smoke of the 3R4F reference cigarette. Similarly, there was an overall reduction in exposure to respiratory as well as reproductive and developmental toxicants from Heatstick aerosols when compared to 3R4F reference cigarette smoke. The combined yield of respiratory toxicants and reproductive/developmental toxicants was 91.7% lower and 94.0% lower, respectively, in Heatstick aerosols compared to the 3R4F reference cigarette. These findings are described further in the toxicological assessment section below.

Findings from FDA's Southeast Tobacco Laboratory (STL)

In order to verify chemical and physical data submitted in the applications, analytical testing of tar, nicotine, acrolein, formaldehyde, and benzo[a]pyrene in mainstream aerosol and ammonia, NNN, and NNK in the tobacco filler was performed at FDA's STL in October 2017. Although there were differences in the analytical methods used by STL and the applicant, the levels of tar, nicotine, and acrolein measured in the aerosol and ammonia, NNK, and NNN measured in the tobacco filler by STL were relatively similar to mean levels reported by the applicant, while the levels of formaldehyde and benzo[a]pyrene were higher than those reported by the applicant. Despite these differences, STL found that IQOS aerosol had substantially lower levels of formaldehyde (77%), and benzo[a]pyrene (90%) compared with the mainstream smoke of the 3R4F reference cigarette.

Published Literature

A search of peer-reviewed literature identified eight additional studies that reported the chemical analysis of the IQOS system with Heatsticks. The data in six of the publications,^{25,26,27,28,29,30} which include nicotine, tar, glycerol, and HPHCs, among other compounds, are consistent with the data reported by the applicant. Only two of the publications, Auer et al.³¹ and Davis et al.,³² were not consistent with the data submitted by the applicant. Auer et al. reported higher levels of several compounds in the IQOS system with Heatsticks compared to combusted cigarettes; however, multiple analytical issues were identified by FDA, limiting interpretation of this study. Davis et al. stated that formaldehyde cyanohydrin was identified in the analysis of the polymer film filter in unused Heatsticks. However, in amendment MR0000114, received on April 26, 2018, the applicant demonstrated that,

²⁵ Farsalinos K, Yannovits N, Sarri T, Voudris V, Poulas K. Nicotine delivery to the aerosol of a heat-not-burn tobacco product: comparison with a tobacco cigarette and e-cigarettes. *Nicotine Tob Res.* 2018 Jul 9;20(8) 1004-1009.

²⁶ Savareear B, Lizak R, Brokl M, et al. Headspace solid-phase microextraction coupled to comprehensive two-dimensional gas chromatography–time-of-flight mass spectrometry for the analysis of aerosol from tobacco heating product. *J Chromatogr.* 2017;1520:135-142.

²⁷ Bekki K, Inaba Y, Uchiyama S, Kunugita N. Comparison of chemicals in mainstream smoke in heat-not-burn tobacco and combustion cigarettes. *J UOEH.* 2017;39(3):201-207.

²⁸ Stephens W. Comparing the cancer potencies of emissions from vapourised nicotine products including e-cigarettes with those of tobacco smoke. *Tob Control.* 2017;0:1-8.

²⁹ Mallock N, Böss L, Burk R, et al. Levels of selected analytes in the emissions of “heat not burn” tobacco products that are relevant to assess human health risks. *Arch Toxicol.* 2018 Jun;92(6):2145-2149.

³⁰ Li X, Luo Y, Jiang X, et al. Chemical analysis and simulated pyrolysis of tobacco heating system 2.2 compared to conventional cigarettes. *Nicotine Tob Res.* 2019 Jan 1;21(1):111-118.

³¹ Auer R, Concha-Lozano N, Jacot-Sadowski I, et al. Heat-not-burn tobacco cigarettes: smoke by any other name. *JAMA Intern Med.* 2014 Jul 1;177:1050-1052.

³² Davis B, Williams M, Talbot P. IQOS: evidence of pyrolysis and release of toxicants from plastic. *Tob Control.* 2019 Jan;28(1):34-41.

based on chromatographic data and literature, the compound that Davis et al. identified as formaldehyde cyanohydrin is likely meso-lactide, a condensation product of lactic acid.

Conclusion

In the most comprehensive study of HPHCs conducted by the applicant, 107 out of 108 HPHCs tested were either found to be below the limit of detection or quantification or lower than the concentrations in mainstream cigarette smoke. Analytical testing data across multiple studies demonstrate that HPHCs are present at substantially lower levels in the aerosol from the IQOS system with Heatsticks compared to mainstream cigarette smoke. With the exception of nicotine and anabasine, HPHCs are 47-99.9% lower in the IQOS system with Heatsticks compared per unit and 20-99.8% lower when compared to normalized nicotine levels. These findings were similar to those produced by STL and found in the published literature. The applicant identified additional compounds across Heatstick variants that are either present exclusively or are found in higher quantities in the aerosol of the IQOS system with Heatsticks compared to the mainstream smoke in the 3R4F reference cigarette. These compounds include menthol-related constituents, alkaloids, and flavors. When assessing the overall yield of compounds on FDA's established list of HPHCs, along with compounds of toxicological concern identified by the applicant not on FDA's HPHC list, the yields of potential carcinogens, respiratory toxicants, and reproductive/developmental toxicants were considerably lower in Heatstick aerosols compared with 3R4F reference cigarette smoke. Despite the increase in some constituents of concern, the substantial reduction across constituents on FDA's HPHC list demonstrates that, on the whole, the process used to heat tobacco in the IQOS system significantly reduces the production of harmful and potentially harmful chemicals compared to cigarette smoke. **Therefore, there is sufficient evidence to support the following proposed modified risk claim: "This [the process of heating tobacco, but not burning it] significantly reduces the production of harmful and potentially harmful chemicals."**

3. Toxicological Assessment

This section summarizes the toxicological studies provided by the applicant to compare the relative toxicity between the IQOS system and combusted cigarettes. A summary of these studies and conclusions are described below. More detailed description and analysis can be found in the Toxicology review.

In Vitro Studies

The applicant submitted in vitro cytotoxicity and mutagenicity assays using OECD guidelines performed with Regular and Fresh Menthol Heatsticks aerosols and 3R4F reference cigarette smoke. The findings from these studies are summarized below and evaluated in depth in the Toxicology review.

Neutral Red Uptake (NRU) Assays

The applicant submitted two separate study reports for NRU assays with aerosols from Regular and Fresh Menthol Heatsticks, as well as smoke from the 3R4F reference cigarette. The NRU is an in vitro assay that can determine cytotoxicity. Mouse embryo cells were used in assays submitted in these applications. These cells were exposed to TPM and gas/vapor phase (GVP) fractions from Heatstick aerosols and 3R4F reference cigarette smoke in separate experiments. The applicant expressed cytotoxicity in the NRU results as the reciprocal of the effective concentration that reduces the number of viable cells by 50%. Under the conditions tested by the applicant in these study reports, cytotoxicity for the TPM and GVP fractions was reduced by 94%-95%, respectively, for both Regular and Fresh

Menthol Heatsticks compared to the reference cigarette on a per stick basis. When normalized to nicotine yield, however, cytotoxicity for the TPM and GVP fractions was reduced by 91%-92%, respectively, for both Regular and Fresh Menthol Heatsticks compared to the reference cigarette. Although the cells used in this NRU cytotoxicity study are validated and useful for general toxicity screening, testing in normal respiratory cell lines would be more relevant and informative for evaluation of inhaled tobacco products.

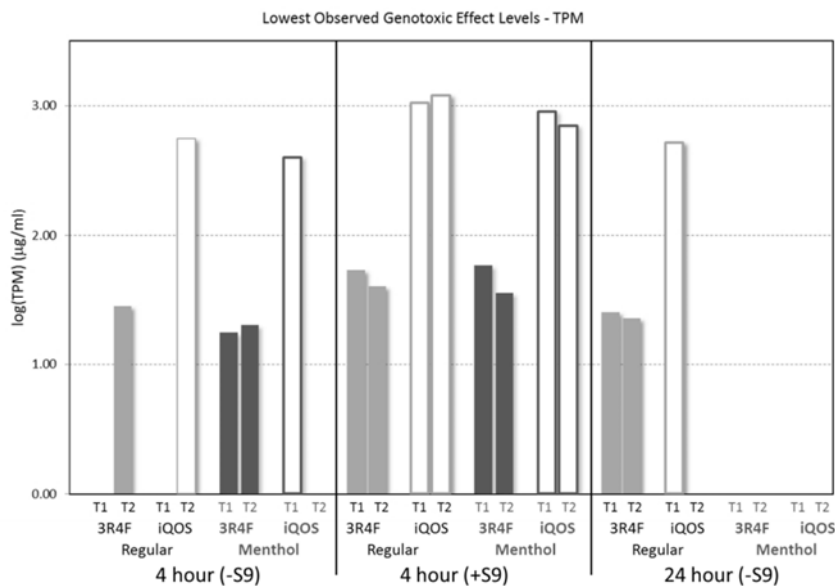
Bacterial Reverse Mutation test (Ames test)

The applicant submitted study reports from Ames tests with TPM from Regular and Fresh Menthol Heatstick aerosols and 3R4F reference cigarette smoke. The Ames test detects chemicals that induce mutations in bacteria that restore the functional capability to synthesize an essential amino acid. In these studies, the applicant exposed five *Salmonella typhimurium* strains to varying concentrations of TPM from Regular and Fresh Menthol Heatstick aerosols and 3R4F reference cigarette smoke for 48-72 hours.

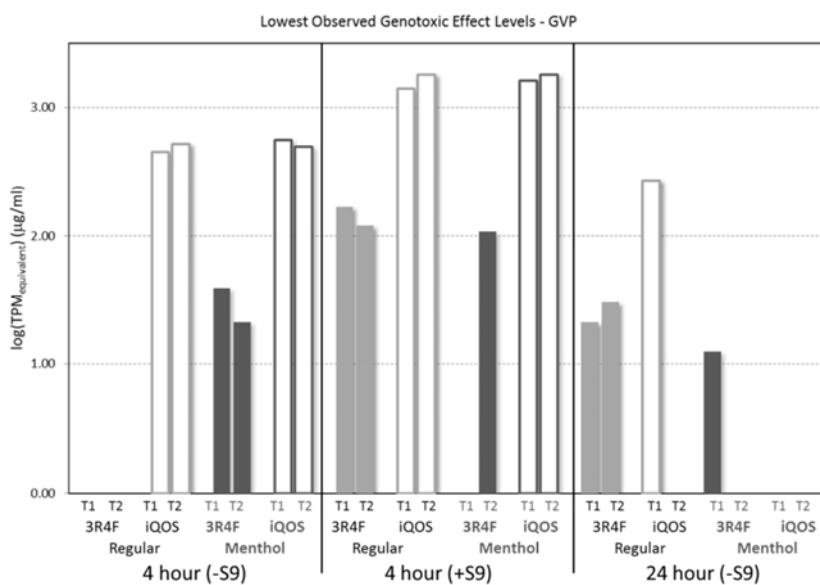
The data in these study reports indicate that TPM from Regular and Menthol Heatstick aerosols did not demonstrate mutagenic potential under the conditions tested in this assay, while TPM from 3R4F reference cigarette smoke did produce a mutagenic response in 3 of the 5 stains tested when combined with metabolic activation. However, the study reports submitted by the applicant did not contain information from an Ames test with GVP from Heatstick aerosols or 3R4F reference cigarette smoke. The HPHC information submitted by the applicant indicates that Heatstick aerosols contain mutagens that are typically found in GVP (e.g., formaldehyde, propylene oxide). As such, an Ames test with GVP from Heatstick aerosols and 3R4F reference cigarette smoke would provide additional information about the mutagenic potential of the products.

Mouse Lymphoma Assay (MLA)

The applicant submitted study reports from mouse lymphoma assays (MLA) conducted with aerosols from Regular and Fresh Menthol Heatsticks, as well as smoke from 3R4F reference cigarettes. The MLA is a qualitative test that can determine clastogenicity and mutagenicity in a mammalian cell line. The in vitro mouse lymphoma assay study reports submitted by the applicant show a biologically relevant mutagenic response in mammalian cells from whole Heatstick aerosols and 3R4F reference cigarette smoke (both with and without metabolic activation) after 4 hours of exposure. However, the applicant indicates that the minimum Heatstick TPM concentration required to produce this positive result was 15 to 30 times greater than the concentration required for TPM from the 3R4F reference cigarette (Figure 2) and 8 to 24 times greater for GVP (Figure 3). This observation should not be construed as a comparison of mutagenic potency. There is no validated method for inferring a quantitative relationship (like potency) from a qualitative measure (like mutagenicity in the MLA).

Figure 2. Lowest observed genotoxic effect levels for TPM

Original image; data source: “RLS-ZRH-2015-252 MLA Reg SR” and “RLS-ZRH-2015-251 MLA Ment SR”

Figure 3. Lowest observed genotoxic effect levels for GVP

Original image; data source: “RLS-ZRH-2015-252 MLA Reg SR” and “RLS-ZRH-2015-251 MLA Ment SR”

Limitations

The applicant indicates that a common generation and collection method was used for the Heatstick aerosols and 3R4F reference cigarette smoke for the in vitro studies submitted (i.e., Ames test, MLA, NRU assay). While the collection techniques were similar for Heatstick aerosols and 3R4F reference cigarette smoke, there were parameters that differed systematically between the products. For

instance, there were differences in numbers of products used in each aerosol collection session, the number of “accumulations” collected, and differing volumes of phosphate-buffered saline for GVP collection. The applicant does not provide any rationale or justification for these differences in TPM or GVP collection and it is unclear what effect these different collection methods have on the in vitro results described above.

It is also important to note that assay limitations affect the conclusions that can be drawn from these in vitro tests. For example, while the Ames assay can robustly detect DNA damage from mutagens that directly interact with DNA, the bacterial strains used in these assays do not possess the complex DNA repair mechanisms that mammalian cells have. Notably, some mutagenic compounds (e.g., acetaldehyde, formaldehyde, benzene) in cigarette smoke that are also found in IQOS aerosol are weakly positive or produce a negative response in the Ames test and yet are known to be either possibly carcinogenic or carcinogenic in humans.

In Vivo Studies

90-Day Nose-only Inhalation Studies

The applicant submitted study reports from two separate 90-day nose-only inhalation studies with adult male and female Sprague-Dawley rats. The first study determined toxicity produced by repeated exposure to either aerosols from Regular Heatsticks, 3R4F reference cigarette smoke, or filtered air (sham control). The second study determined whether menthol altered the toxicity produced by repeated exposure to Heatstick aerosols. In this study, rats were repeatedly exposed to aerosols from either Fresh Menthol Heatsticks, smoke from the 3R4F reference cigarette, smoke from one of two mentholated versions of the 3R4F reference cigarette, or filtered air (sham control). All rats were exposed to their assigned condition 6 hours each day for 90 days. After the 90-day exposure period, a subset of these rats was provided a 42-day post-exposure recovery period.

The findings from these studies indicate that repeated exposure to 3R4F reference cigarette smoke affected body weight, increased presence of proinflammatory markers in the lungs, produced some evidence of liver toxicity, affected differential blood counts, and altered lung physiology. These changes were either not observed or were significantly less severe in rats repeatedly exposed to Heatstick aerosols. Similarly, while rats exposed to Heatstick aerosols exhibited histopathological changes like hyperplasia, metaplasia, and tissue degeneration, those changes were generally less severe than those observed in rats exposed to reference cigarette smoke. In addition, biomarkers of exposure to HPHCs were typically lower in rats exposed to Regular and Fresh Menthol Heatstick aerosols than in rats exposed to 3R4F reference cigarette smoke, and were similar to the sham control.

Sub-chronic inhalation studies, like the 90-day inhalation studies provided by the applicant, can provide important information about non-cancer toxicology endpoints, but these studies are not generally sensitive enough to determine systemic toxicities from chronic tobacco product use. Despite that, the data submitted by the applicant indicate that sub-chronic exposure to Heatstick aerosols produce fewer or less severe histopathological changes than sub-chronic exposure to similar concentrations of 3R4F reference cigarette smoke.

18-month Carcinogenicity Study with A/J Mice

The applicant conducted a carcinogenicity study with male and female A/J mice. The primary aim of the study was to determine whether lung tumor incidence is lower in sham controls and groups exposed to Heatstick aerosols than in the group exposed to the same concentration of 3R4F reference cigarette

smoke after 18 months. Mice were exposed to fresh air (sham controls), 3R4F reference cigarette smoke, or Heatstick aerosol 6 hours each day, 5 days each week using a whole-body exposure study design. The study with female mice lasted 18 months, while the study with male mice was halted after 15 months because of low survival in the group exposed to the Heatstick aerosol. The final carcinogenicity study report for the products on MR0000059, MR0000060, MR0000061, and MR0000133 was submitted in amendment MR0000128.

In the study, there were no statistically significant differences in incidence of any tumor type measured between sham controls and mice exposed Heatstick aerosols, regardless of the sex of the mouse or the concentration tested. Female mice repeatedly exposed to 3R4F reference cigarette smoke exhibited significantly higher incidence of multiple tumor types (e.g., laryngeal papilloma, bronchioloalveolar adenoma, bronchioloalveolar adenoma and carcinoma combined) when compared to sham controls and female mice exposed Heatstick aerosols. The applicant also found that the mean number of tumors in female mice exposed to 3R4F cigarette smoke was significantly larger than sham controls or female mice exposed to Heatstick aerosols. For male mice, there were no statistically-significant differences in tumor multiplicity between sham controls and the group exposed to Heatstick aerosols.

The applicant indicates that the A/J mouse strain was chosen for this study because it is “highly susceptible to lung tumor development and has been widely used as a screening system in carcinogenicity testing.” The major limitation of the A/J mice as a model of smoking-induced lung carcinogenesis is that only a small increase in lung tumors over background is observed in this highly susceptible mouse strain. Moreover, this pulmonary response is not specific to cigarette smoke. Many agents which are not considered lung carcinogens induce lung tumors in this strain.³³ Given the especially high background tumor incidence, it is not clear whether a 5-day/week, whole-body exposure paradigm that continues for 18 months is appropriate for the strain of mouse used in this study. In addition, the exposure protocol differed by sex (5 groups of female mice vs 2 groups of male mice), which limited interpretation. As a result, this study provides inconclusive results regarding the carcinogenic potential of Heatstick aerosols.

FDA received amendment MR0000168 on December 20, 2019, which provided a detailed review of the applicant’s finding of low survival rates observed in male A/J mice in amendment MR0000128. The applicant argues that the comparatively low survival of male mice reported in amendment MR0000128 is attributable to urogenital tract impairment and related to mouse strain, sex, age, and other unidentified environmental factors. The evidence submitted by the applicant is consistent with this hypothesis and is not refuted by the scientific literature that is currently available.

Nicotine Pharmacokinetic Study

The applicant submitted a study in Sprague-Dawley rats with the objective to model inhalation of the nicotine-containing aerosol, conversion of nicotine to cotinine in the liver, distribution of nicotine and cotinine between the blood and liver compartments, and cotinine excretion from repeated exposure to 3R4F reference cigarette smoke or Heatstick aerosols. However, a lack of study power and insufficient sampling time points limited the ability to detect significant group differences. This study was not informative for the purposes of assessing the potential health effects of the IQOS system.

³³ Stoner GD. Lung tumors in strain A mice as a bioassay for carcinogenicity of environmental chemicals. *Exp Lung Res.* 1991;17:405-423.

Systems Toxicology Studies

Acute and Repeated Exposure Studies with Human Organotypic Tissues

The applicant submitted data from five separate in vitro organotypic studies assessing the effects of acute and repeated exposure to Regular Heatstick aerosols and 3R4F reference cigarette smoke on human gingival, buccal, nasal, bronchial, and coronary arterial epithelium cultures. The organotypic studies submitted by the applicant indicate that both 3R4F reference cigarette smoke and Regular Heatstick aerosols produce evidence of toxicity in human gingival, bronchial, buccal, nasal, and small airway tissues, as well as epithelial tissues from human coronary arteries. These toxic effects included cytotoxicity, changes in xenobiotic metabolism, evidence of oxidative stress and DNA damage, and increased levels of proinflammatory mediators. The applicant also presents data indicating that both 3R4F reference cigarette smoke and Regular Heatstick aerosols produce functional genomic changes in the tissues tested.

Overall, Heatstick aerosols generally produced fewer pathophysiological changes and adverse effects than reference cigarette smoke in studies with human organotypic tissues or produced similar toxicity at higher concentrations. In addition, while Heatstick aerosols produced pro-inflammatory effects and adverse pathophysiological effects in buccal cell cultures and altered responses to oxidative stress in gingival cell cultures, those changes are less pronounced than effects from the 3R4F reference cigarette smoke and generally occurred at higher concentrations. Also, Heatstick aerosols increased cell adhesion and reduced monocyte migration in coronary artery cell cultures at higher concentrations than 3R4F reference cigarette smoke.

However, there are significant issues and concerns about the experimental approach taken in these studies that limit the conclusions that can be drawn from these data. In most of the studies provided, the applicant used methods that are non-validated towards understanding risk; were non-standardized; and are unknown as to their reliability and, consequently, their applicability towards regulatory use to determine the effects of acute exposure to either 3R4F reference cigarette smoke or Regular Heatstick aerosols on naïve tissues. Also, the tissues used in these studies were taken from single individuals, which dramatically reduces genetic variability and, therefore, the ability to extrapolate across the population. Information drawn from these studies does not inform the evaluation of public health consequences of chronic exposure Regular Heatstick aerosols in a diverse population with a history of cigarette smoking.

ApoE^{-/-} Mouse Switching Study

The applicant also submitted a study report from an eight-month-long switching and cessation study with female ApoE^{-/-} mice. This study included mice exposed to filtered air, reference cigarette smoke, or Heatstick aerosols 5 days a week for 8 months. The study also included a group that was exposed to reference cigarette smoke for 2 months followed by 6 months of filtered air to model smoking cessation, and a group that was exposed to reference cigarette smoke for 2 months followed by 6 months of Heatstick aerosol to model switching from cigarettes to Heatsticks.

The histopathological findings from this study indicate that 8 months of reference cigarette smoke exposure increased emphysema score, an index of respiratory toxicity selected by the applicant. However, similar histopathological characteristics were not seen in other exposure groups. These data suggest that switching to Heatstick aerosols after a relatively brief period of exposure to reference cigarette smoke produces histopathological changes that are similar to cessation. It is unclear, however, whether switching from longer or intermittent periods of cigarette smoke exposure would produce

similar results. Repeated exposure to either 3R4F reference cigarette smoke or Heatstick aerosols produced other physiological effects; however, the severity was generally greater in the cigarette group.

There are several limitations to this study design that may limit interpretability. These include using only female mice when evidence from studies with a different mouse strain (i.e., A/J mice) indicates that males may be more sensitive to the toxic effects of Heatstick aerosols. Also, the period of 3R4F reference cigarette smoke exposure was likely too brief to determine how Heatstick aerosols affect progression of long-term toxic effects caused by 3R4F reference cigarette smoke.

Toxicological Assessment of Other Constituents in IQOS

The applicant included a limited toxicological evaluation of the 80 chemicals found exclusively in Heatstick aerosols or at higher concentrations than in 3R4F reference cigarette smoke. As described above, the applicant reported 4 possible or probable human carcinogens, 19 other chemicals that generated structural alerts in the OECD QSAR toolbox, and 9 additional chemicals identified in the applicant's literature review as being of toxicological concern. Each of these chemicals was reported at higher concentrations in the aerosol of the IQOS system with Heatsticks compared to 3R4F reference cigarette smoke.

In order to assess the significance of this increase in constituents, the toxicological reviewer conducted comparisons of the total concentration of carcinogens, respiratory toxicants, and reproductive or developmental toxicants between Heatstick aerosols and the smoke of the 3R4F reference cigarette. For carcinogenicity, the concentration of carcinogens from FDA's established HPHC list was combined with the concentration of those compounds identified as mutagenic, genotoxic, or potentially carcinogenic in the literature review provided by the applicant and compounds that produced an alert for genotoxicity, mutagenicity, or carcinogenicity in the predictive toxicology assay reported by the applicant. Overall, the concentration of these established and potential carcinogens was reduced by approximately 82% in the Heatstick aerosol relative to the smoke of the 3R4F reference cigarette.

Similarly, there is an overall reduction in exposure to respiratory as well as reproductive and developmental toxicants from Heatstick aerosols when compared to 3R4F reference cigarette smoke. The combined yield of respiratory and reproductive/developmental toxicants was 91.7% and 94.0% lower, respectively, in Heatstick aerosols compared to the 3R4F reference cigarette smoke. These toxicants include both HPHCs on the established list and potential respiratory or reproductive and developmental toxicants not on the HPHC list but identified by the applicant in its screening studies (MR0000097 and MR0000116).

Although this method of comparing overall yields is limited by the lack of information on the potency and mode of action of each chemical compound, it provides, at least, an assessment of the magnitude of difference in the presence of harmful and potentially harmful chemicals, including those not currently on FDA's HPHC list.

Conclusion

Although systematic differences in collection methods between Heatstick aerosols and reference cigarette smoke contribute to some uncertainty in the interpretation of study findings, the in vitro evidence submitted indicates that Heatstick aerosols had reduced cytotoxic and mutagenic potential when compared to 3R4F reference cigarette smoke. In vivo evidence indicates less severe histopathological changes in rats exposed to Heatstick aerosols compared with reference cigarette smoke. In addition, Heatsticks generally produced fewer pathophysiological changes and adverse effects

than reference cigarette smoke in studies with human organotypic tissues or produced similar toxicity at higher concentrations. When assessing the overall yield of compounds on FDA's established list of HPHCs, along with compounds of toxicological concern identified by the applicant not on FDA's HPHC list, the yields of potential carcinogens, respiratory toxicants, and reproductive/developmental toxicants were considerably lower in Heatstick aerosols compared with 3R4F reference cigarette smoke. Overall, data from the nonclinical studies submitted by the applicant suggest that IQOS aerosol has lower toxic potential than cigarette smoke under the conditions used in the assays and for the endpoints measured. However, significant limitations of these studies noted in the Toxicology review limit stronger conclusions about the relative health risks of using the IQOS system.

4. Clinical Assessment

In this section, the clinical studies provided by the applicant to examine BOEs and biomarkers of potential harm (BOPHs) resulting from switching from combusted cigarettes to IQOS are assessed. A summary of these studies and conclusions is presented below. More detailed description and analysis can be found in the Medical, Epidemiological, and Behavioral and Clinical Pharmacology reviews.

Biomarkers of Exposure (BOEs)

The applicant conducted four clinical "reduced exposure" (REX) studies, including two 5-day confinement studies conducted in Poland and Japan and two 90-day ambulatory studies (with a 5-day confinement) conducted in Japan and the U.S. (see Table 2). The main objective of the studies was to demonstrate that the products that are the subject of these applications result in reduced exposure to HPHCs compared with combusted cigarettes. In each of the studies, participants were randomized to one of three study arms: continued smoking of combusted cigarettes (CC, n=40), switch to Tobacco Heating System 2.2 (THS 2.2³⁴, referred to as IQOS in this document) (n=80), or switch to smoking abstinence (n=40). In the two 5-day studies, participants used products in a confined setting and biomarkers were measured on each of the 5 days to assess changes in biomarkers over time and differences among the three study arms. In the two 90-day studies, participants used products in a confined setting for 5 days (biomarkers were measured on each of the 5 days) and then used products for 85 days in an ambulatory setting.

Table 2. Human clinical "reduced exposure" (REX) research studies included in the MRTPAs

Study ID (Location)	Tobacco Product Flavor	Study Design
ZRHR-REXC-03-EU (Poland)	Non-menthol	Randomized, controlled, open-label, 3-arm parallel group design with multiple use days (5 days confined)
ZRHR-REXC-04-JP (Japan)	Non-menthol	Randomized, controlled, open-label, 3-arm parallel group design with multiple use days (5 days confined)
ZRHM-REXA-07-JP (Japan)	Menthol	Randomized, controlled, open-label, 3-arm parallel group design with multiple use days (5 days confined, 85 days ambulatory)
ZRHM-REXA-08-US (U.S.)	Menthol	Randomized, controlled, open-label, 3-arm parallel group design with multiple use days (5 days confined, 85 days ambulatory)

³⁴ IQOS is the commercial version of THS 2.2.

The applicant assessed changes in systemic exposure to 17 HPHCs and their metabolites (including nicotine) in study participants. The exposure biomarkers selected correspond with 14 of the 20 HPHCs identified by the FDA for reporting that are found in cigarette smoke or filler³⁵ (Table 3). In addition, the studies assessed 1-hydroxypyrene (which is considered a proxy for PAHs in general), 2-hydroxyethylmercapturic acid (HEMA), and o-Toluidine (an aromatic amine). Exposures to acetaldehyde, formaldehyde, isoprene and ammonia were not assessed as biomarkers due to the lack of suitable biomarkers for these exposures. Also, no heavy metals were measured (e.g., arsenic, cadmium, lead), presumably because of the long half-lives of these biomarkers. The list of all selected biomarkers, their classes, and related major toxicities is presented in Table 3. Systemic exposure to nicotine is discussed in section III.C.1.

Table 3. Biomarkers of exposure (BOEs) measured in REX Studies and their corresponding HPHC, chemical class, and toxicity class

HPHC	Chemical Class	Selected BOE	Toxicity Class			
			Carcinogenic	Cardiovascular	Respiratory	Reproductive
Acrolein	Carbonyl	3-hydroxypropylmercapturic acid (3-HPMA) ¹		X	X	
Acrylonitrile	Acid derivatives	2-cyanoethylmercapturic acid (CEMA) ³	X		X	
4-Aminobiphenyl	Aromatic amines	4-aminobiphenyl (4-ABP) ³	X			
Benzene	Aromatic hydrocarbon	S-phenylmercapturic acid (S-PMA) ¹	X	X		X
Benzo[a]pyrene	PAH	3-hydroxybenzo[a]pyrene (3-OH-B[a]P) ³	X			
1,3-Butadiene	Aliphatic dienes	Monohydroxybutenyl-mercapturic acid (MHBMA) ¹	X	X		X
Carbon monoxide (CO)	Gas	blood carboxyhemoglobin (COHb) ^{1,2} and exhaled CO ² (eCO)				X
Crotonaldehyde	Carbonyl	3-hydroxy-1-methylpropyl-mercapturic acid (3-HMPMA)	X			
Ethylene oxide	Epoxide	2-hydroxyethylmercapturic acid (HEMA) ³	X		X	X
1-Aminonaphthalene	Aromatic amines	1-aminonaphthalene (1-NA) ³	X			
2-Aminonaphthalene	Aromatic amines	2-aminonaphthalene (2-NA) ³	X			
Nicotine	Alkaloids	Nicotine equivalents (NEQ) Plasma nicotine ^{2,3} , cotinine ^{2,3}				X
NNK	Nitrosamines	total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (total NNAL) ¹	X			
NNN	Nitrosamines	total N-nitrosornicotine (total NNN) ³	X			
o-Toluidine	Aromatic amines	o-toluidine ³	X			
Pyrene ⁴	PAH	total 1-hydroxypyrene (1-HOP) ³	X			
Toluene	Aromatic hydrocarbon	S-benzylmercapturic acid (S-BMA) ³			X	X

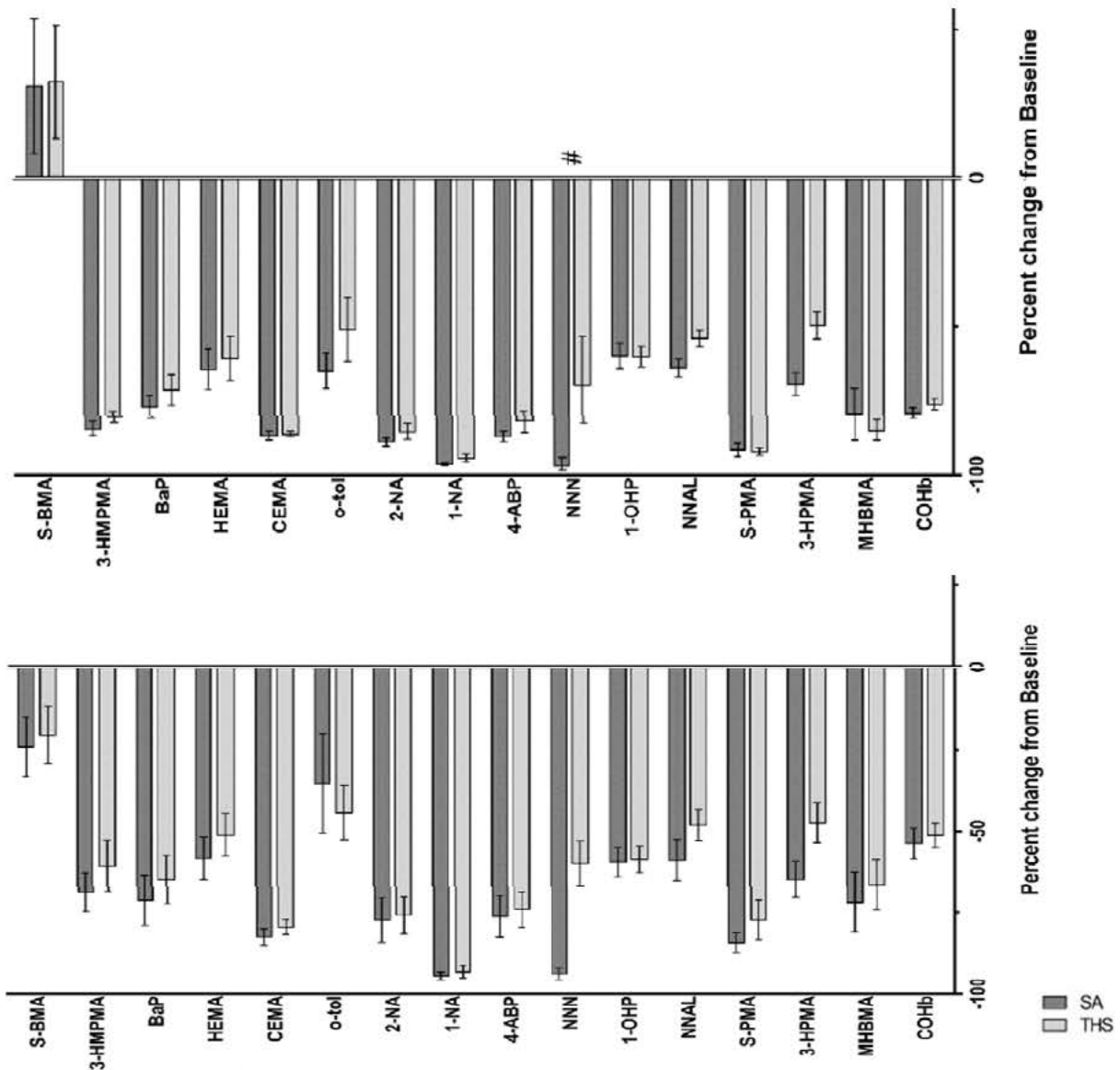
¹Primary endpoints; ²BOE not measured in urine; ³Secondary endpoints; ⁴Pyrene is not on HPHC list but its metabolite 1-HOP serves as a surrogate for PAHs in general. Toxicity class designations are from FDA's HPHC list. Source: FDA generated.

³⁵ See: <https://www.fda.gov/TobaccoProducts/Labeling/RulesRegulationsGuidance/ucm297786.htm>

Main Findings

The four REX studies showed that systemically measured BOEs to HPHCs were statistically significantly (p values < 0.05) reduced among smokers completely switching to THS 2.2 with BOE levels similar to the participants in the SA arm. At the end of the five-day controlled switching period (in confinement) from CC to THS 2.2 use, systemic exposure to 15 of 16 selected BOEs decreased by 47-96%. Results for urinary S-BMA levels were mixed; they were elevated in study ZRHR-REXC-03-EU and reduced in study ZRHR-REXC-04-JP. Figure 4 shows a comparison of mean percent changes from baseline to Day 5 in BOEs measured between THS 2.2 and SA arms for studies ZRHR-REXC-03-EU and ZRHR-REXC-04-JP.

Figure 4. Percent change in BOEs from baseline geometric mean levels (and 95% CIs) at Day 5 in ZRHR-REXC-03-EU (upper panel) and ZRHR-REXC-04-JP (lower panel)



Source: MRTPAs section 6.1.3.2.

For the menthol products, by the end of the 90-day ambulatory period, decreases in systemic levels of BOEs were less pronounced, possibly due to decreased compliance or other reasons associated with the differences in the populations. The changes from the GM baseline values were in the range of 34-92% (ZRHM-REXA-07-JP) and 15-82% (ZRHM-REXA-08-US) and all changes remained statistically significant.

Statistically significant reductions of systemic exposure to 15 HPHCs, or their biomarkers, after switching from CC to THS 2.2 were demonstrated in all REX studies. The exposures to S-BMA, a biomarker of o-toluene, were not different among the THS 2.2, CC, and SA arms. This is most likely due to environmental sources of exposure to this biomarker. The profiles of decline of the other BOEs observed in the THS 2.2 arm were similar to those observed in the SA arm.

Limitations

It is important to note a few limitations to these studies. Of the studies with ambulatory periods, the Japanese study (ZRHM-REXA-07-JP) had high compliance and thus provided convincing evidence of BOE reduction. However, the compliance in the SA arm of the U.S. study (ZRHM-REXA-08-US) was poor and the variability was high; thus, the results from the SA arm of this study should be interpreted with caution. However, the assessment at Day 5 (in confinement) provides the clearest indication of the short-term reductions in exposure of *completely switching* from cigarettes to the IQOS system.

In the 90-day studies, the applicant did not estimate the percent change in biomarker concentrations in the subset of participants who did not completely switch to THS 2.2 and were dual users of THS 2.2 and cigarettes at Day 90. However, in a 6-month study (received on June 11, 2018 and described further in the section below), the applicant presented the changes in biomarkers among dual users (defined as “ ≥ 1 THS or CC and $1\% \leq \text{THS} < 70\%$ over the entire analysis period or THS-use and CC-use on $< 50\%$ of the days in the analysis period”). BOE reductions at 6 months among dual users (vs. CC) were much smaller as compared with THS (vs. CC), suggesting that risk is unlikely to be substantially reduced as a result of exposure reduction in dual users of cigarettes and THS.

Although the applicant measured BOEs that reflect the major classes of HPHCs, BOEs were not assessed for the following compounds on the abbreviated HPHC list: acetaldehyde, formaldehyde, isoprene, ammonia, arsenic, cadmium, and lead. As described above, FDA is not aware of established biomarkers for acetaldehyde, formaldehyde, isoprene and ammonia, and biomarkers for heavy metals (such as arsenic, cadmium, and lead) typically have longer half-lives. The applicant elsewhere reported that aerosol concentrations for these constituents are lower than cigarette smoke, but the magnitude of exposure reduction from complete switching is unclear. The applicant also did not assess BOEs for the compounds found to be elevated in the aerosol of Heatsticks compared with 3R4F reference cigarette smoke, including those compounds identified as of toxicological concern.

Biomarkers of Potential Harm (BOPHs)

All REX studies (described above) included measurements of several BOPHs as secondary or exploratory study endpoints to determine if THS 2.2 use resulted in biological changes that may indicate a change in long-term disease risk. The BOPHs were selected based on key mechanisms of the major smoking-associated diseases, namely cardiovascular disease (CVD), chronic obstructive pulmonary disease (COPD), and lung cancer. Markers of oxidative stress (8-iso-F2-isoprostane-alpha (8-epi-PGF2 α) and thromboxane metabolites) and inflammation (white blood cell count (WBC), c-reactive protein (CRP), soluble intercellular adhesion molecular 1 (sICAM-1), fibrinogen) were selected due to their role in the development and progression of these three major smoking-related diseases. Additionally, disease-

specific endpoints were selected for CVD (carboxyhemoglobin, lipid profile and oxysterols, HbA1c, and blood pressure), lung function (FEV₁), and cancer (biomarkers of exposure). The applicant specified six of the BOPHS as representative of mechanisms underlying the diseases of interest:

Assessed in all four studies:

- *8-iso-15(S)-Prostaglandin F2α (8 epi-PGF2α)* – a measure of oxidative stress
- *11-dehydrothromboxane B2 (11-DTX-B2)* – associated with platelet activation

Assessed in ambulatory studies:

- *High Density Lipoprotein-Cholesterol (HDL-C)* – a measure of lipid metabolism
- *White blood cell (WBC) count* – a marker of inflammation
- *Soluble intercellular adhesion molecule-1 (sICAM-1)* – a measure of endothelial dysfunction
- *Forced expiratory volume in the first second (FEV₁)* – a measure of lung function

Markers of Inflammation

Across the biomarkers of inflammation, only WBC count and sICAM-1 demonstrated some differences in the two 90-day studies for the THS 2.2, CC, and SA arms. There was a reduction in WBC counts over the course of the studies. Reductions were generally largest in the SA arm, but there were consistent reductions approaching similar levels in THS 2.2 arms. In the Japanese study, THS 2.2 use resulted in reduced WBC counts, as early as Day 30, to levels similar to those seen in the SA arms. The U.S. study results are difficult to interpret because of the small sample size. The study length is a limiting factor for interpretations because WBC reductions are optimally detected between 6 and 10 months after smoking cessation. In the two 90-day studies, smokers in the THS 2.2 arm had lower sICAM-1 levels than participants in the CC arm after adjusting for baseline sICAM-1 levels, sex, and baseline CC consumption. The sICAM-1 levels in the THS 2.2 arm (approximately 8.5-10.5% reduced from baseline values) were similar to the SA arm. These reductions were generally seen within the first 30 days of exposure and were maintained throughout the ambulatory period.

Markers of Oxidative Stress

The markers for oxidative stress included 8-epi-PGF2α and 11-DTX-B2. Smokers who switched to THS 2.2 showed more than a 12% reduction in 8-epi-PGF2α levels compared with smokers who continued to smoke combusted cigarettes; however, these reductions were not conclusive due to high variability in the data. Although 11-DTX-B2 levels were reduced for smokers who switched to THS 2.2, the differences were not statistically significant. The U.S. study findings were confounded by non-compliance with product use (in both the THS 2.2 and SA arms), compared with the Japanese study, resulting in a reduced sample size and a greater-than-expected variability in 11-DTX-B2 results.

Markers of Potential Cardiovascular Risks

Cardiovascular risks were assessed by measurements of blood lipids, triglycerides, apolipoprotein B, and blood pressure in the REX studies with the ambulatory period. Cardiovascular risk biomarkers did not change significantly over the course of the ambulatory periods, except for HDL-C. Smokers who switched to THS 2.2 had higher HDL-C levels compared to smokers who continued to smoke CC. In the Japanese study, the HDL-C levels in the THS 2.2 arm were similar to the SA arm after adjusting for baseline HDL-C levels, sex, and CC consumption at baseline. In the U.S. study, HDL-C levels in the CC arm were similar to those in the SA arm; however, only nine of the 40 participants randomized to the SA arm reported adherence to SA, making results of the U.S. study difficult to interpret.

Markers of Lung Function

Spirometry measurements were included primarily as a safety measure. In the Japanese study, smokers who switched to THS 2.2 had a non-statistically significant increase of 1.91% of predicted value in their FEV₁ compared to smokers who continued to smoke CC, with no notable differences between the THS 2.2 and SA arms. However, studies of a longer duration (at least 6 to 12 months) would be necessary to fully assess the impact of THS 2.2 use on FEV₁. In the U.S. study, vital capacity was the only lung function test where a small but notable difference (0.10 L) was observed between the THS 2.2 and SA arms. There were no other notable differences in gas transfer, lung volume, or spirometry parameters between the THS 2.2 and CC arms.

Markers of Genotoxicity and Mutagenicity

Several indirect measures evaluated cancer-specific endpoints. Potential reduction in cancer development risk relates to reduced exposure to carcinogens, as well as reductions in CYP450 1A2 activity and urine mutagenicity. Cytochrome CYP450 1A2 is a key factor in the activation metabolism of various constituents, including carcinogens such as heterocyclic amines, mycotoxins, nitrosamines, and aryl amines, found in tobacco smoke, and can thus be indicative of exposure to tobacco smoke. Its activity is induced by PAHs generated by tobacco smoke.

CYP450 1A2 activity at baseline was markedly different among the REX studies, ranging from 70- 122%, with the lowest values in the Japanese populations and highest in the U.S. population (due to differences in genetic factors and smoking behavior). In participants who switched to THS 2.2, CYP450 1A2 activity was statistically significant lower (decreased by 30-36%) compared to participants who continued to smoke CC on Day 5; these reductions were similar or lower than levels during the ambulatory period on Day 90 (range of 21-32%), and the changes in the SA arms were of similar magnitude. In the REX studies, the baseline urine mutagenicity levels were highly variable; however, there was a clear trend to decreased urine mutagenicity values in the THS 2.2 arm on Day 5 (by 47% to 72%); these differences were sustained in the ambulatory period and were similar to changes in the SA arm. The results observed indicate a lower level overall of mutagenic compounds in the urine of THS 2.2 users compared to the CC arm.

Amendment with 6-Month Follow-up Study Results

Received on June 11, 2018, amendment MR0000117 from PMP S.A. was the final report for a 6-month randomized, open-label, 2-arm, parallel group, multi-center study of IQOS. The study enrolled 984 healthy adult U.S. smokers and compared biological and functional changes between those who continued to smoke vs. those who switched completely or incompletely to THS 2.2. As compared to the two previous 90-day ambulatory studies conducted in Japan and the U.S., the 6-month clinical study had “several differences, namely, the duration of the exposure period was much longer, the study follow up was conducted in a more real-life setting (i.e., no confinement), and there was a much larger number of participants in the study to allow us to more accurately to describe product use patterns in a more diverse study population” (Study Results Overview).

Markers of inflammation, lung function (FEV₁), and other BOPs measured in the exposure reduction studies did not change appreciably in the two 90-day studies. However, the 6-month study observed that 5 out of the 8 primary endpoints showed a statistically significant change in smokers who switched from cigarette smoking to THS use (as defined by the applicant) including HDL-C, WBC count, FEV₁, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL), and carboxyhemoglobin (COHb). The endpoints are markers of lipid metabolism, inflammation, oxygen transport, lung function, and carcinogen exposure. When comparing the “per protocol” results in the 6-month study with those of the 90-day

studies, the magnitude of differences between THS and CC were similar for HDL-C, WBC, 11-DTX-B2, COHb, and FEV₁. The percent reductions (THS vs. CC use) for sICAM-1 and 8-epi-PGF2 α were slightly lower in the 6-month study compared with the 90-day studies, while for NNAL, the reductions were higher in the 6-month study compared with the 90-day studies.

Limitations

While the BOPHS selected by the applicant were based on key mechanisms of the major smoking-associated diseases, not all of the endpoints may have been appropriate for the length of the study. For example, the applicant acknowledged that changes in CRP and lung function would require longer study durations. In the 90-day studies, the results are inconclusive for many of the BOPHS that required a longer study duration to detect changes. Some of these limitations were addressed in the 6-month study amendment (received on June 11, 2018), but some of the endpoints may take even longer to change.

The findings from the 6-month study should be interpreted with caution. The study arms became imbalanced at Month 6, given that the subjects who were the basis for the primary analysis in each arm are a subset of the subjects who were the basis of randomization in each arm. Therefore, the use of multiple comparisons for the eight biomarkers performed with Hailperin-Ruger statistical method was not justified. Furthermore, the data analyses assumed that the individual outcomes (i.e., changes in the BOEs and BOPHS) were independent; however, their independence was not tested and may not necessarily be true. Therefore, study interpretation is limited.

Although the BOPHS can be informative for key mechanisms of smoking-related disease, they are not replacements for clinical endpoints (e.g. CVD, cancer, COPD). In general, questions remain about the credibility of BOPHS as surrogate endpoints or substitutes for disease endpoints.^{36,37} Nevertheless, besides serving as surrogates for disease, BOPHS in studies assessing tobacco products are still informative for other purposes, particularly for enhancing “confidence that there is no worsening risk, in the least.”³⁸

Conclusion

The four 5-day studies demonstrated that complete switching from combusted cigarettes to the IQOS system resulted in reduced exposure to HPHCs, with a magnitude of decline similar to complete smoking abstinence. Despite issues with compliance (i.e., use of other tobacco products), reductions in BOEs among complete switchers were also seen in 90-day studies conducted in Japan and the U.S. Findings from the clinical studies suggest a significant reduction in BOEs to 15 HPHCs when smokers switch completely to IQOS. The reduced BOEs reflect a range of chemical and toxicity classes. Although BOEs are not available for every constituent on the HPHC list, the comparative aerosol data provided demonstrate that many other HPHCs are significantly reduced compared to combusted cigarette smoke. **Based on this evidence, there is a substantial reduction in exposure to HPHCs when users of IQOS switch completely from combusted cigarettes to IQOS. Thus, there is sufficient evidence to support**

³⁶ Institute of Medicine Committee to Assess the Science Base for Tobacco Harm Reduction. In: Stratton K, Shetty P, Wallace R, Bondurant S, eds. *Clearing the Smoke: Assessing the Science Base for Tobacco Harm Reduction*. Washington, DC: National Academies Press; 2001.

³⁷ Chang CM, Cheng YC, Cho M, et al. Biomarkers of potential harm: summary of an FDA-sponsored public workshop. *Nicotine Tob Res.* 2019 Jan 1;21(1):3-13.

³⁸ Institute of Medicine Committee to Assess the Science Base for Tobacco Harm Reduction. In: Stratton K, Shetty P, Wallace R, Bondurant S, eds. *Clearing the Smoke: Assessing the Science Base for Tobacco Harm Reduction*. Washington, DC: National Academies Press; 2001.

the following proposed modified risk claim: “Scientific studies have shown that switching completely from conventional cigarettes to the IQOS system significantly reduces your body’s exposure to harmful or potentially harmful chemicals.” Eight of the 9 voting members of TPSAC agreed that the exposure reduction claim was substantiated, finding the nonclinical and clinical data compelling and that the significant reduction in the levels of HPHCs in IQOS compared to combusted cigarettes and significant reduction in biomarkers of exposure made the proposed claim accurate.

It should be noted that the applicant did not assess BOEs for the compounds found to be elevated in the aerosol of Heatsticks compared with 3R4F reference cigarette smoke, including those compounds identified as of toxicological concern. **While it is possible that some harmful exposures could increase, these exposures are unlikely to significantly impact the substantial reduction in exposure to HPHCs found when cigarette smokers switch completely to IQOS.**

The clinical studies did not directly measure disease endpoints, but rather, measured BOPHS. Biomarkers in general have limited credibility as surrogate endpoints or substitutes for disease endpoints, but may serve to provide supportive information. Overall, the REX studies demonstrated minor improvements in some BOPHS in the THS 2.2 arm relative to the CC arm; however, the clinical significance of the changes is unclear. In general, substantial differences were not observed, potentially because the chosen markers were not observed for a sufficient duration, were not tobacco specific, or were not adequately sensitive to detect changes in pharmacologic endpoints. It is also unclear how predictive the chosen biomarkers are of long-term tobacco-related disease risk. Therefore, although switching completely to the IQOS system may decrease exposure to BOEs, longer-term studies are needed to evaluate the overall health impact.

5. Assessment of Potential Health Risks to Tobacco Users and Non-Users

In this section, the evidence from the chemistry, non-clinical, and clinical findings is integrated to assess the potential health risks of use of the IQOS system with Heatsticks among current tobacco users and non-users.

Health Risks Compared to Combusted Cigarettes

Complete Switching from Cigarettes to IQOS

As described above, the available scientific evidence shows that the IQOS system produces lower concentrations of many HPHCs compared to cigarette smoke and the non-clinical data suggests a favorable toxicological profile of the IQOS system compared to combusted cigarettes. However, the clinical studies conducted by the applicant were not sufficient to demonstrate that completely switching from combusted cigarettes to the IQOS system reduces the risk of tobacco-related disease or harm. In the two 90-day studies, the BOPHS measured did not change appreciably across continued smokers, complete switchers to IQOS, and smoking abstinence. The 6-month study resulted in some significant differences in BOPHS, but the clinical significance of these changes is unclear. In addition, the proposed claims are exceedingly broad in their reference to “tobacco-related diseases” and “harm” in general. Cigarette smoking is a cause of many diseases and harms and the relationship between increased consumption and disease risk varies.

In addition, as described in section III.C.1, the abuse liability of the IQOS system does not appear to be appreciably different than combusted cigarettes, which is consistent with the applicant’s conclusion: “Based on the totality of available evidence covering abuse liability domains from THS product features, likelihood of use and consequence of use, THS shares a similar abuse liability [to] conventional

cigarettes.” Similar abuse liability signifies that the IQOS system can sustain addiction in nicotine-dependent populations and, in non-users, can have a similar risk of initiation and developing addiction as combusted cigarettes, thereby providing no support for a general claim about reduced risk of harm.

Although the evidence is not sufficient to demonstrate that complete switching reduces the risk of tobacco-related disease or harm, the evidence does demonstrate that complete switching from cigarettes to IQOS can result in substantially reduced exposure to many HPHCs. Whether the reductions in BOEs are reasonably likely to result in a measurable and substantial reduction in morbidity or mortality depends on many factors, including the magnitude of reduction and the specific disease endpoint. On one end, complete cessation of smoking has been shown to result in the reduced risk of many different tobacco-related diseases as compared with continued smoking in long-term epidemiological studies.³⁹ While the applicant concluded that the exposure reductions were similar to those of smoking cessation, the evidence from the exposure reduction clinical studies and product chemistry studies demonstrates that the exposures to HPHCs are not completely eliminated with the use of the products that are the subject of these applications. In addition, there may be increased exposures to some constituents of toxicological concern, as demonstrated by the findings from the applicant’s non-targeted differential screening study.

Epidemiological studies evaluating disease risk associated with reductions in smoking intensity have been inconsistent. For example, some studies have observed significant reductions in lung cancer risk associated with substantial (>50%) reductions in cigarettes smoked per day.^{40,41} However, other studies did not observe a change in disease or mortality risk with smoking intensity reduction.^{42,43,44,45} The lack of consistent findings may be due, in part, to variations in definition of smoking reduction, differences in the dose-response relationship by disease endpoint, and the potential for smoking compensation among self-reported reducers across published studies.

Different dose-response relationships between smoking and disease endpoints also have implications for whether disease risk would decrease with reduced smoking. For example, while lung cancer and COPD generally have linear dose-response relationships with smoking, CVD risk has a non-linear relationship with smoking for which “even low levels of exposure to tobacco, such as a few cigarettes per day, occasional smoking, or exposure to secondhand tobacco smoke are sufficient to substantially increase risk of cardiac events”.⁴⁶ Thus, while a reduction in smoking may decrease risk of some diseases, as suggested for lung cancer, it may not decrease risk of other tobacco-related diseases.

³⁹ IARC. IARC Handbooks of Cancer Prevention, Tobacco Control. Vol. 11: Reversal of Risk After Quitting Smoking. Lyon, France; 2007.

⁴⁰ Godtfredsen NS, Prescott E, Osler M. Effect of smoking reduction on lung cancer risk. *JAMA*. 2005;294(12):1505-1510.

⁴¹ Song YM, Sung J, Cho HJ. Reduction and cessation of cigarette smoking and risk of cancer: a cohort study of Korean men. *J Clin Oncol*. 2008;26(31):5101-5106.

⁴² Tverdal A, Bjartveit K. Health consequences of reduced daily cigarette consumption. *Tob Control*. 2006;15(6):472-480.

⁴³ Godtfredsen NS, Holst C, Prescott E, Vestbo J, Osler M. Smoking reduction, smoking cessation, and mortality: a 16-year follow-up of 19,732 men and women from The Copenhagen Centre for Prospective Population Studies. *Am J Epidemiol*. 2002;156(11):994-1001.

⁴⁴ Godtfredsen NS, Osler M, Vestbo J, Andersen I, Prescott E. Smoking reduction, smoking cessation, and incidence of fatal and non-fatal myocardial infarction in Denmark 1976-1998: a pooled cohort study. *J Epidemiol Community Health*. 2003;57(6):412-416.

⁴⁵ Hart C, Gruer L, Bauld L. Does smoking reduction in midlife reduce mortality risk? Results of 2 long-term prospective cohort studies of men and women in Scotland. *Am J Epidemiol*. 2013;178(5):770-779.

⁴⁶ Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention, Office on Smoking and Health. Publications and Reports of the Surgeon General. *How Tobacco Smoke Causes Disease: The Biology and Behavioral Basis for*

Dual Use of Cigarettes and IQOS

The evidence is not sufficient to demonstrate that dual use of combusted cigarettes and the IQOS system, the most commonly reported pattern of use in the observational studies described below, is associated with a meaningful reduction in exposure or disease risk. In the 90-day studies, the applicant did not estimate the percent change in biomarker concentrations in the subset of participants who were dual users. The 6-month study showed that incomplete switchers or dual users (as defined by the applicant) had much smaller reductions in exposure biomarkers as compared with IQOS use, suggesting that disease or mortality risk is unlikely to be substantially reduced as a result of exposure reduction in dual users of cigarettes and IQOS.

Health Risks Compared to No Tobacco Use

Evidence submitted by the applicant suggests that long-term use of the IQOS system is likely to produce significant health risks when compared with not using any tobacco products. Although exposure to HPHCs is significantly lower than that associated with use of combusted cigarettes, users of the IQOS system would still be exposed to many HPHCs. For example, consuming 10 Heatsticks exposes users to levels of carcinogenic and reproductive toxicant HPHCs, acetaldehyde, acetamide, acrylamide, ammonia, catechol, formaldehyde, mercury, and propylene oxide that are comparable to smoking 1-3 cigarettes. In addition, several compounds were found to be at higher concentrations in IQOS aerosol than cigarette smoke, including 4 possible or probable human carcinogens, 19 other chemicals that generated structural alerts in the QSAR, and 9 additional chemicals identified in the applicant's literature review as being of toxicological concern.

In order to put the BOE findings into context, FDA epidemiologists conducted an analysis comparing biomarker levels observed in the applicant's clinical studies with that of the PATH Study Wave 1 (2013-14) participants with biomarker data who were never tobacco users and former smokers. In this analysis, several biomarkers among complete switchers in the applicant's clinical studies were found to be reduced to levels comparable to those of PATH Study never tobacco users and former smokers (e.g., 3-HPMA, a biomarker of acrolein exposure; NNN; and 1-hydroxypyrene, a biomarker of pyrene exposure), while others were elevated (e.g., NNAL, a biomarker of NNK exposure; CYMA, a biomarker of acrylonitrile exposure).

Exposure to HPHCs at levels similar to a few cigarettes per day is relevant to assessing health risks because epidemiological studies have found that even low intensity smoking can increase the risks of all-cause mortality, lung cancer, and CVD when compared to never smoking.^{47,48,49} Additionally, the health effects due to nicotine exposure may not be substantially different between use of IQOS and cigarettes, including risks to the fetus and the potentially negative effect of nicotine on the developing brain in youth.

Smoking-Attributable Disease: A Report of the Surgeon General. Atlanta, GA: Centers for Disease Control and Prevention (US); 2010.

⁴⁷ Inoue-Choi M, Liao LM, Reyes-Guzman C, Hartge P, Caporaso N, Freedman ND. Association of long-term, low-intensity smoking with all-cause and cause-specific mortality in the National Institutes of Health-AARP Diet and Health Study. *JAMA Intern Med.* 2017;177(1):87-95.

⁴⁸ Bjartveit K, Tverdal A. Health consequences of smoking 1-4 cigarettes per day. *Tob Control.* 2005;14(5):315-320.

⁴⁹ Rosengren A, Wilhelmsen L, Wedel H. Coronary heart disease, cancer and mortality in male middle-aged light smokers. *J Intern Med.* 1992;231(4):357-362.

This is consistent with the findings from non-clinical studies, which showed that, although IQOS aerosol produces a favorable toxicological profile, it can still produce damage in in vitro and in vivo models. For example, Heatstick aerosol produced cytotoxicity and mutagenicity in mammalian cell lines and rats exposed to Heatstick aerosols exhibited histopathological changes like hyperplasia, metaplasia, and tissue degeneration, though the changes were generally less severe than those observed in rats exposed to reference cigarette smoke.

Conclusion

Although the non-clinical data suggests a favorable toxicological profile of the IQOS system compared to combusted cigarettes, significant limitations were noted in the toxicological review of these studies that limit stronger conclusions about the relative health risks of using the IQOS system. The clinical studies conducted by the applicant demonstrated that completely switching from combusted cigarettes to IQOS reduces exposure to many HPHCs; however, they were not sufficient to demonstrate that completely switching from combusted cigarettes to the IQOS system reduces the risk of tobacco-related disease or harm. The FDA discipline reviews that assessed the scientific accuracy of the claims about the risk of tobacco-related disease or harm (Toxicology, Behavioral and Clinical Pharmacology, Medical, Epidemiology) found that they were not substantiated. I agree with their conclusions. In addition, there was near unanimous agreement by TPSAC that the applicant did not demonstrate the proposed claim *“Scientific studies have shown that switching completely from cigarettes to the IQOS system can reduce the risks of tobacco-related diseases.”* TPSAC was divided on whether there was scientific support for the claim *“Switching completely to IQOS presents less risk of harm than continuing to smoke cigarettes.”* Some argued that they thought of “harm” as broader than “tobacco-related disease” and therefore supportable. Others, however, did not think the nonclinical and clinical data provided demonstrated reduced harm. **Overall, there is insufficient evidence to support the proposed modified risk claim *“Scientific studies have shown that switching completely from conventional cigarettes to the IQOS system can reduce the risks of tobacco-related diseases.”* or *“Switching completely to IQOS presents less risk of harm than continuing to smoke cigarettes.”***

Although the applicant has not demonstrated that the products, as actually used, will significantly reduce harm and the risk of tobacco-related disease to individual tobacco users, under section 911(g)(2) of the FD&C Act, FDA may issue an exposure modification order if, among other findings, it determines that the scientific evidence that is available “demonstrates that a measurable and substantial reduction in morbidity or mortality among individual tobacco users is reasonably likely in subsequent studies.” The assessment of whether the exposure reduction observed with complete switching from cigarettes to the IQOS system is likely to translate into a measurable and substantial reduction in morbidity and mortality is ultimately a matter of judgement based on indirect evidence. This was reflected in TPSAC’s discussion and vote. The 5 voting members who did not think the applicant had demonstrated that the reductions in exposure were reasonably likely to translate to a measurable and substantial reduction in morbidity and mortality focused their discussion on the lack of demonstration—or lack of direct evidence supporting reductions in morbidity and mortality. Several members noted that although the results were in the right direction (i.e., suggested reductions in disease), these results were not statistically significant. The 2 voting members who voted “yes” said they did so assuming that such a large reduction in exposure would likely result in reduction in disease, even if that was not demonstrated in the short-term studies submitted by the applicant. The applicant provided compelling evidence that the IQOS system does not combust tobacco and accompanying aerosol data showing dramatic reductions across a wide range of HPHCs identified by FDA. The applicant also demonstrated that BOEs to many HPHCs dropped significantly and approached the levels seen with complete

cessation. Although the use of the IQOS system clearly still exposes users to HPHCs and would be expected to cause harm, such dramatic changes in exposure relative to combusted cigarettes are reasonably likely to, in general, translate to lower risk of tobacco-related morbidity and mortality. **Although reduced risk has not been demonstrated, the totality of evidence presented suggests that a measurable and substantial reduction in morbidity or mortality among individual tobacco users is reasonably likely in subsequent studies.** Smaller reductions in BOEs among incomplete switchers or dual users suggest disease or mortality risk is unlikely to be substantially reduced if there is dual use of combusted cigarettes and IQOS.

Evidence submitted by the applicant suggests that long-term use of the IQOS system is likely to produce significant health risks when compared with not using any tobacco products. Despite a favorable toxicological profile, Heatstick aerosols produced cytotoxicity and mutagenicity in mammalian cell lines, and rats exposed to Heatstick aerosols exhibited histopathological changes like hyperplasia, metaplasia, and tissue degeneration. In addition, because health effects due to nicotine exposure are not expected to be substantially different between the IQOS system and combusted cigarettes, IQOS may pose potentially negative effects on the developing brain in youth. Several members of TPSAC expressed this concern as well, recommending that the inclusion of nicotine and risk of addiction be communicated to consumers. It should be noted that under section 910(c)(1)(B) of the FD&C Act and in accordance with section 202(a) of the Family Smoking Prevention and Tobacco Control Act, FDA's marketing authorization order for the IQOS system (PM0000424-PM0000426, PM0000479) requires inclusion of the warning statement "WARNING: This product contains nicotine. Nicotine is an addictive chemical." on the package labels of all Heatsticks packs and on all kits containing Heatsticks packs as well as in all advertisements for such products and kits.

B. Consumer Understanding and Perceptions

1. Labels, Labeling, and Advertising (LLA) with Proposed Modified Risk Information

The applicant developed and tested LLA materials that include the proposed modified risk claims on IQOS brochures, Heatstick packs, and direct mail communications. The applicant also provided other examples of promotional channels that it may use to inform smokers about the product, such as print and digital ads, age-restricted digital and social media channels, and package inserts and onsets on combusted cigarette packs (such as Marlboro cigarettes) that would direct smokers to an IQOS website.

2. Consumer Studies

The applicant submitted two qualitative and five quantitative studies related to consumer understanding of the proposed modified risk claims. Several of the studies were qualitative and quantitative studies that helped inform development of the proposed claims that were tested in PBA-05. PBA-05 studies quantitatively assessed consumers' responses to the applicant's proposed LLA materials with its proposed modified risk claims, and study PMTA05-NOC served as a control study in which the LLA materials did not contain the proposed claims.

Each PBA-05 and PMTA-05-NOC study examined one of three claims, or no claim, as follows:

- PBA-05-RR1: Reduced Risk Claim 1
- PBA-05-RR2: Reduced Risk Claim 2
- PBA-05-REC: Reduced Exposure Claim

- PMTA-05-NOC: None of the three proposed claims.

On its LLA materials, the applicant proposes to include the SG Warnings currently used for cigarettes. The applicant also tested alternate versions of its LLA materials that contained self-designed “Important Warnings” (hereafter referred to as “PMI Warnings”). As shown in Table 4, there were three different “PMI Warnings,” with each version corresponding to one of the applicant’s three proposed modified risk claims. For LLA materials with reduced risk claims 1 and 2, the PMI Warnings state that using IQOS still presents risks and that cessation is the best way for smokers to reduce their risks. For LLA materials with the reduced exposure modified risk claim, the PMI Warning states that switching to IQOS has not been shown to reduce disease risk. All three PMI Warnings also state that Heatsticks contain nicotine, which is addictive. The PMI Warnings do not describe specific negative consequences, aside from addiction, caused by using IQOS. Rather, they refer to risk, harm, and tobacco-related diseases generally.

Table 4. Surgeon General (SG) warnings and PMI warnings tested in the applicant’s consumer perception studies

Proposed Modified Risk Claim	PMI Warning	SG Warnings
(Reduced Risk Claim 1) “AVAILABLE EVIDENCE TO DATE: • The IQOS system heats tobacco but does not burn it. • This significantly reduces the production of harmful and potentially harmful chemicals. • Scientific studies have shown that switching completely from conventional cigarettes to the IQOS system can reduce the risks of tobacco-related diseases.”	“IMPORTANT WARNING: • Reduced risk does not mean no risk. The best way to reduce your risk of tobacco-related diseases is to completely quit tobacco use. • HeatSticks™ contain nicotine, which is addictive. • Using the IQOS system can harm your health.”	One of the following displayed in rotating fashion: • “SURGEON GENERAL’S WARNING: Quitting Smoking Now Greatly Reduces Serious Risks to Your Health.” • “SURGEON GENERAL’S WARNING: Smoking By Pregnant Women May Result in Fetal Injury, Premature Birth, And Low Birth Weight.” • “SURGEON GENERAL’S WARNING: Cigarette Smoke Contains Carbon Monoxide.” [†] • “SURGEON GENERAL’S WARNING: Smoking Causes Lung Cancer, Heart Disease, Emphysema, And May Complicate Pregnancy.”
(Reduced Risk Claim 2) “AVAILABLE EVIDENCE TO DATE: Switching completely to IQOS presents less risk of harm than continuing to smoke cigarettes.”	“IMPORTANT WARNING: • Less risk of harm does not mean no risk of harm. The best way to reduce your risk of tobacco-related diseases is to completely quit tobacco use. • HeatSticks™ contain nicotine, which is addictive.”	
(Reduced Exposure Claim) “AVAILABLE EVIDENCE TO DATE: • The IQOS system heats tobacco but does not burn it. • This significantly reduces the production of harmful and potentially harmful chemicals. • Scientific studies have shown that switching completely from conventional cigarettes to the IQOS system significantly reduces your body’s exposure to harmful and potentially harmful chemicals.”	“IMPORTANT WARNING: • It has not been demonstrated that switching to the IQOS system reduces the risk of developing tobacco-related diseases compared to smoking conventional cigarettes. • HeatSticks™ contain nicotine, which is addictive. • Using the IQOS system can harm your health.”	

[†] Note: FDA’s PMTA authorization for these products requires the removal of the CO Warning and the addition of a warning stating, “WARNING: This product contains nicotine. Nicotine is an addictive chemical.” Source: FDA. *PMTA Marketing Order: FDA Submission Tracking Numbers (STNs): PM0000424-PM0000426, PM0000479*. Silver Spring, MD: U.S. Food & Drug Administration; 2019. <https://www.fda.gov/media/124248/download>

Each study had the same four objectives: to assess responses to IQOS labeling and marketing material, including:

- (1) comprehension of the IQOS material
- (2) risk perceptions of IQOS and four comparator objects (combusted cigarettes, e-cigarettes, nicotine replacement therapies [NRTs], cessation)
- (3) intent to use various products (IQOS, combusted cigarettes, e-cigarettes, any nicotine-containing products)
- (4) change in intention to quit all tobacco, including combusted cigarettes

The first three aims were assessed among former smokers, never smokers, and current smokers with and without an intention to quit smoking combusted cigarettes, while the fourth aim was only assessed in current smokers with an intention to quit combusted cigarettes. In this section, we present findings related to the first two objectives (consumer comprehension and risk perceptions). Section III.C. discusses findings related to intention to use the IQOS system.

In section III.A. of this review, it was determined that the proposed reduced exposure claim is substantiated, but the proposed reduced risk claims are not. As a result, the assessment of the impact of the modified risk claims on consumer understanding and perceptions is focused on the proposed reduced exposure claim. Accordingly, this section focuses primarily on the results from the studies that evaluated the proposed reduced exposure claim (PBA-05-REC) and no claim (PMTA-05-NOC).

In evaluating consumer understanding, the focus is on two key outcomes: perceived health risks and perceived addiction risk.

Overall Perceptions of Health Risks

First, in assessing whether consumers understand the modified risk information in the context of total health, one important consideration is to ensure that consumers do not interpret a reduced exposure claim to mean “no risk.”

In the “no claim” study where participants were exposed to LLA materials without the proposed modified risk claims, adult consumers generally rated the health risks of using IQOS as lower than smoking combusted cigarettes and slightly higher than e-cigarette use. After viewing IQOS LLA materials with the reduced exposure claim, adult consumers perceived IQOS as presenting moderate risks to health, including risks of an array of tobacco-related diseases and conditions (see Figure 5). In the PBA-05-REC study, on a 100-point scale (from 0=“no risk” to 100=“very high risk”), adult smokers with no intention to quit smoking rated the risks of using IQOS as 44.4 (95% CI: 40.6-48.1). Ratings were somewhat higher for the other groups, ranging from 49.3 (smokers with an intention to quit) to 58.7 (young adult never smokers).

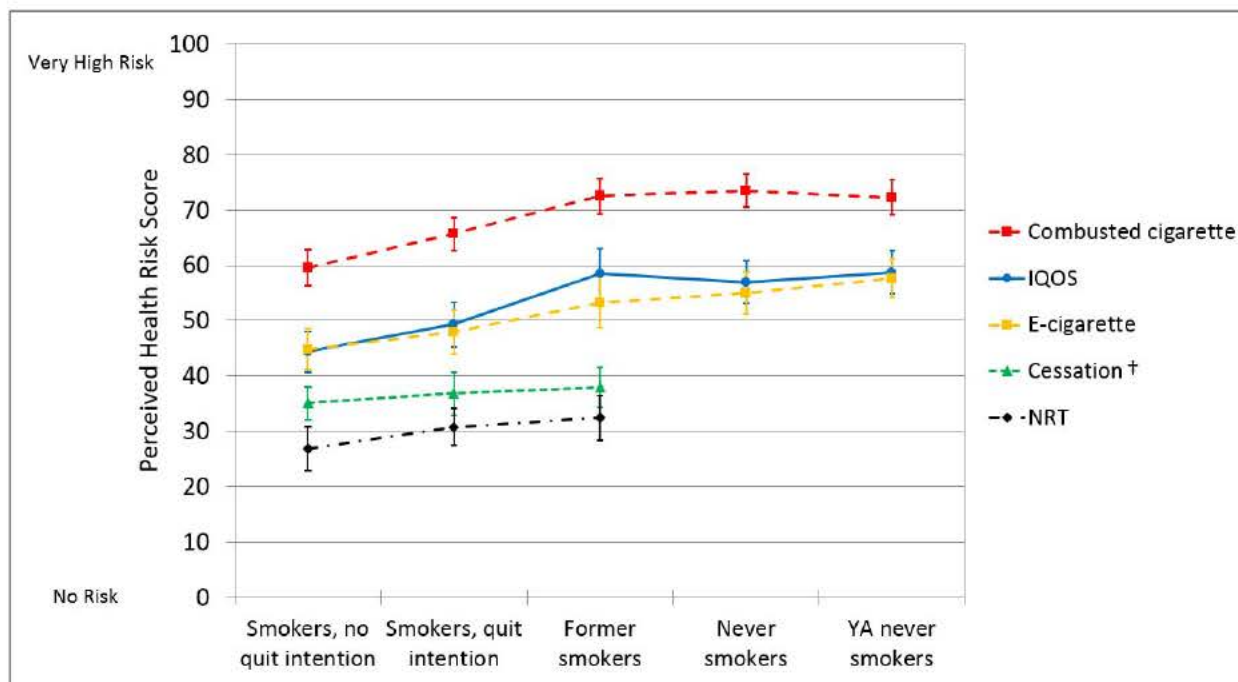
These results suggest that adult consumers accurately perceive IQOS as harmful to health.

Perceptions of Health Risks Compared with Smoking Combusted Cigarettes

Next, in assessing whether consumers adequately understand the modified risk information in the context of total health, reviewers also considered whether consumers’ perceptions of risk from IQOS vs. combusted cigarettes were in line with the findings discussed above (section III.A.).

After viewing IQOS LLA materials both with and without the proposed modified risk claims, including with the reduced exposure claim, adult consumers rated the health risks of using IQOS as lower than those of smoking combusted cigarettes, which is consistent with the relative health risks of the product that are reasonably likely (see section III.A). For example, in the PBA-05-REC study, using the applicant's 0-100 scale of perceived health risk, smokers with no intention to quit rated IQOS 15.2 points lower than combusted cigarettes after viewing an IQOS brochure containing the reduced exposure claim (Figure 5). Note that these estimates were from studies in which LLA materials contained SG Warnings rather than PMI Warnings. The difference between average ratings of health risk from IQOS and combusted cigarettes (among all smoker groups) was slightly larger in studies where participants viewed LLA materials with the reduced exposure claim, compared to the study where participants viewed LLA materials with none of the proposed claims. For example, in the brochure condition, the difference between ratings of combusted cigarettes and IQOS was 3.3-5.8 points greater (on the 100-point scale of perceived health risk) when the IQOS brochure contained the reduced exposure claim rather than no claim. This pattern of results suggests that consumers perceive IQOS as less harmful than combusted cigarettes in the absence of exposure to modified risk claims and that the reduced exposure claim may have lowered some people's perceived risk of using IQOS compared to smoking combusted cigarettes. However, as discussed below, because the applicant examined these conditions in separate studies rather than via random assignment in a single study, reviewers were limited in their ability to attribute these differences solely to the claim itself.

Figure 5. Perceived health risks of IQOS and use of other products after viewing IQOS brochure with reduced exposure claim and Surgeon General's (SG) warnings



Source: Brochure condition with Surgeon General Warning in REC study (based on data in THS-PBA-05-REC-US Study Report Appendix 15.2 Tables, pp. 77-79). Bars represent 95% CIs. † Refers to the risks that remain because you smoked cigarettes. YA = Young Adults.

Perceptions of Addiction Risks Compared with Smoking Combusted Cigarettes

To assess whether consumers adequately understand the modified risk information in the context of total health, reviewers also considered whether the proposed claims may mislead consumers into thinking that the products present a lower risk of addiction (i.e., lower addictive potential and abuse liability) than combusted cigarettes.

After viewing IQOS LLA materials (with SG Warnings) with or without the reduced exposure claim, adult consumers perceived IQOS as less addictive than combusted cigarettes. For example, using the 0-100 scale, the difference in ratings of addictiveness for combusted cigarettes vs. IQOS in the “no claim” study ranged from 11.0 points among adult former smokers to a 20.3-point difference among adult smokers intending to quit. Note, when adult former smokers, never smokers, and young adult never smokers viewed LLA materials with the reduced exposure claim, perceived addictiveness of IQOS was slightly lower compared to participants who viewed materials with none of the proposed claims. These findings indicate that consumers perceive IQOS as less addictive than combusted cigarettes and that the proposed claim may further contribute to this misperception. As discussed below, this misperception of the addictiveness of IQOS has been addressed by FDA in its PMTA orders for these products, which require the inclusion of a nicotine addictiveness warning on all IQOS LLA.

Perceptions of Health Risks Compared with Smoking Cessation and NRT Use

To assess whether consumers adequately understand the modified risk information in the context of total health, we also considered whether the proposed claims may mislead smokers into thinking that using the products would present lower health risks compared to quitting smoking and using NRT instead.

After viewing IQOS LLA materials with the reduced exposure claim, adult smokers rated the health risks of using IQOS as higher than the health risks of quitting smoking and using NRT instead, and adult former smokers rated the health risks of using IQOS as higher than the health risks of using NRT. For current smokers, regardless of which LLA material they viewed (i.e., brochure, Heatstick pack, or direct mail), the perceived health risk of IQOS was significantly higher than the perceived health risk of NRT within each of the current smoker groups. For example, when smokers intending to quit viewed a brochure with the reduced exposure claim and SG Warnings, ratings of risk were $M_{IQOS} = 49.3$ (95% CI: 45.3-53.3) and $M_{NRT} = 30.8$ (95% CI: 27.4-34.1).

These results suggest consumers have an appropriate understanding that the risks of IQOS use are greater than those of smoking cessation and NRT.

Limitations

Participants in the quantitative consumer perception studies were more highly educated than the general U.S. adult population. For example, across studies, the proportion of respondents with at least some college was well above the rate among the U.S. population, according to U.S. Census data. These differences should be kept in mind when considering how the findings may generalize to the U.S. adult and smoker populations.

The applicant did not randomize participants to view LLA materials with or without the proposed modified risk claims, so it is not possible to directly attribute differences in perceptions to the presence of modified risk information. Instead, findings were obtained by comparing results from one study (PMTA05-NOC) with those from other studies (e.g., PBA-05-REC). As a result, it is possible that other differences across studies – aside from the presence or absence of the proposed claims – may account for observed differences across studies (e.g., participant characteristics, study timing). However, there is reason to believe that the findings across the studies can be compared, since each study had a similar design, used a diverse set of study locations, had a large sample size, and was completed within 14 months of the other studies. In addition, interpretations are based on visual inspection of estimates and their confidence intervals, rather than statistical hypothesis testing.

Across the applicant's qualitative and quantitative studies, one limitation is the lack of information on the extent to which smokers understand the need to switch completely to IQOS in order to achieve the reduction described in the claim. The claim itself, however, specifies that "switching completely" to IQOS is how one reduces their exposure. However, the studies did not directly evaluate the extent to which consumers understood this. For instance, the applicant did not assess what smokers believe about the health effects of *partially* switching from combusted cigarettes to IQOS. The applicant submitted no information about whether providing the proposed modified risk claims would either improve or harm smokers' understanding of the health effects of partially switching to IQOS. Given that adult smokers perceive IQOS as presenting lower health risks than combusted cigarettes, they might expect to obtain at least some health benefit from substituting Heatsticks for some--but not all--of their combusted cigarettes. Indeed, studies have found that many smokers seek to limit or cut down on their cigarettes per day, not just as a step toward quitting, but also because of their belief that doing so reduces their health risks.^{50,51,52,53,54} As described above, dual use of cigarettes and the IQOS system is not likely to provide a benefit over exclusive smoking. Thus, it is important that consumers understand that partially switching from combusted cigarettes to IQOS may not result in the benefits communicated in the proposed reduced exposure claim.

Conclusion

Although it is not possible to directly attribute differences in perceptions to the presence of modified risk information because the applicant did not randomize participants to view the LLA materials with or without the modified risk claims, the consumer perception studies conducted by the applicant found that after viewing LLA materials with the reduced exposure claim, consumers perceived IQOS as a tobacco product that presents moderate risks of a wide range of tobacco-related disease and health effects. Consumers also perceived risks associated with use of the product to be lower than those presented by smoking combusted cigarettes, which is in line with the relative health risks of the product that are reasonably likely. Adult smokers accurately rated the health risks of using IQOS as higher than the health risks of quitting smoking and using NRT instead, and adult former smokers accurately rated the health risks of using IQOS as higher than the health risks of using NRT. Similar patterns were

⁵⁰ Cheong Y, Yong HH, Borland R. Does how you quit affect success? A comparison between abrupt and gradual methods using data from the International Tobacco Control Policy Evaluation Study. *Nicotine Tob Res.* 2007;9(8):801-810.

⁵¹ Graham H, Flemming K, Fox D, Heirs M, Sowden A. Cutting down: insights from qualitative studies of smoking in pregnancy. *Health Soc Care Community.* 2014;22(3):259-267.

⁵² Hughes JR, Callas PW, Peters EN. Interest in gradual cessation. *Nicotine Tob Res.* 2007;9(6):671-675.

⁵³ McNeill A. Harm reduction. *BMJ.* 2004;328(7444):885-887.

⁵⁴ Shiffman S, Hughes JR, Ferguson SG, Pillitteri JL, Gitchell JG, Burton SL. Smokers' interest in using nicotine replacement to aid smoking reduction. *Nicotine Tob Res.* 2007;9(11):1177-1182.

observed for participants who viewed LLA materials without the proposed reduced exposure claim, although the difference between perceived health risks of IQOS use and combusted cigarettes tended to be greater for participants who viewed the proposed claim.

Based on the findings of section III.A. regarding the health risks of IQOS, the results of applicant's consumer perception studies support that consumers generally comprehend the modified risk information in the context of total health. In particular, the results indicate that consumers understand that the product is not without risks and that it is more harmful than quitting smoking. Consumers also generally perceive the product as less harmful than combusted cigarettes, which is in line with the relative health risks of the product that are reasonably likely. It is important to note that perceptions of lower risk than combusted cigarettes were observed even in the absence of the reduced exposure claim. This suggests that there may be features of the product other than the LLA that lead consumers to perceive the product as less harmful than combustible cigarettes.

This assessment deviates from the conclusion drawn from TPSAC, which unanimously voted that the applicant did not demonstrate that consumers accurately understand the risks of IQOS after viewing the modified risk information. However, the committee did not identify specific concerns with the findings submitted by the applicant. Moreover, the committee was not asked to consider understanding of each claim independently, so it is unclear whether the committee was considering the reduced exposure claim specifically. One of the few members to detail his rationale explained that the applicant had not shown the modified risk information *increased* comprehension of the message. Section 911(h)(1), however, states "that any advertising or labeling concerning modified risk products enable the public to comprehend the information concerning modified risk and to understand the relative significance of such information in the context of total health and in relation to all of the diseases and health-related conditions associated with the use of tobacco products." **Overall, the evidence that consumers, after viewing LLA materials with the proposed modified risk information, understand IQOS to be a product with likely moderate risks of a range of tobacco-related diseases and a considerably greater risk than quitting smoking and using NRT instead supports comprehension of the proposed modified risk claim in the context of total health.**

One concern about consumer comprehension was the perception that IQOS is less addictive than combusted cigarettes, even though the behavioral and pharmacological evaluations of the applicant's data indicate that IQOS is expected to have an addictive potential and abuse liability similar to combusted cigarettes. This misperception was present among participants who did not view any of the proposed modified risk claims. However, under section 910(c)(1)(B) of the FD&C Act and in accordance with section 202(a) of the Family Smoking Prevention and Tobacco Control Act, FDA's marketing authorization order for the IQOS system (PM0000424-PM0000426, PM0000479) requires inclusion of the warning statement "WARNING: This product contains nicotine. Nicotine is an addictive chemical." on the package labels of all Heatsticks packs and on all kits containing Heatsticks packs as well as in all advertisements for such products and kits. This warning was required to mitigate the potential for consumer misperception of the addiction risk of IQOS.

Another potential concern relates to consumer understanding of the health risks of the product relative to combusted cigarettes. Under section 911(g)(2), for FDA to issue an exposure modification order, FDA must find that the applicant has demonstrated, among other findings, that the labeling and marketing of the product will not *mislead* consumers into believing that the product *is or has been demonstrated* to be less harmful, or *presents or has been demonstrated* to present less of a risk of disease than one or more other commercially marketed tobacco products. As discussed above, consumers generally perceived the product as less harmful relative to cigarettes, whether they were shown the product with

a reduced exposure claim or not. This may be due, at least in part, to the novel design of the IQOS system. These risk perceptions are in line with the relative health risks of the product that are reasonably likely. FDA considered whether including a disclaimer on product labeling and advertising would improve consumer understanding (e.g., improve understanding that although risk reduction is reasonably likely, it has not yet been demonstrated in scientific studies). Specifically, as part of a set of “PMI warnings” in its consumer perception study, the applicant tested the impact of a disclaimer that states “It has not been demonstrated that switching to the IQOS system reduces the risk of developing tobacco-related diseases compared to smoking conventional cigarettes.” As described in the social science review, the applicant reported that there was a significant increase in the participants responding that switching completely to IQOS “has not been demonstrated to reduce risk” when viewing the PMI warnings.

However, the study design limited the inferences that can be drawn in several important ways. First, the response options in the study item were not mutually exclusive, making the results challenging to interpret. Second, the response option that the applicant defined as correct (“has not been demonstrated...”) was worded very similarly to the statement in the PMI warnings itself, suggesting that participants who viewed it may have selected this response option by recognizing the wording of the statement without understanding its meaning (i.e., that the reduction in users’ exposure to harmful and potentially harmful chemicals is reasonably likely to lead to a measurable and substantial reduction in morbidity or mortality, but this has not yet been demonstrated). Finally, the applicant tested these PMI warnings in place of the SG’s warnings, rather than the impact of a disclaimer in addition to the SG warnings, as it would actually be marketed. It is unclear how the disclaimer may affect consumers’ understanding of the product’s disease risks when displayed alongside the SG Warnings that are also required for IQOS. Moreover, the currently available evidence for tobacco products suggests that disclaimers are often limited in their effectiveness,^{55,56,57} and accordingly, I do not expect a disclaimer would improve consumer understanding.

As discussed above, although the studies in the applications were not sufficient to demonstrate actual risk reduction at this time, the totality of the evidence supports that risk reduction is reasonably likely to be demonstrated in subsequent studies. In other words, consumer understanding is in line with the relative health risks of the product that are reasonably likely and testing of actual consumer perception shows that consumers will not be misled about the state of the evidence regarding the relative health risks of the product. Overall, the available evidence demonstrates that consumers generally understand the relative health risks of the product that are reasonably likely, which would be expected to impact behavior in a way that promotes public health.

Finally, there is a potential concern related to consumer understanding of the difference between exclusive IQOS use and dual use of IQOS with other tobacco products. The applicant’s proposed exposure reduction claim specifies that smokers can obtain the stated exposure benefits by switching completely to IQOS, but the applicant did not provide evidence related to consumer understanding of this component of the information and the need to use IQOS exclusively. As discussed by TPSAC, the applicant did not assess how consumers perceive the health risks associated with *partially* switching

⁵⁵ Baig SA, Byron MJ, Lazard AJ, Brewer NT. “Organic,” “natural,” and “additive-free” cigarettes: comparing the effects of advertising claims and disclaimers on perceptions of harm. *Nicotine Tob Res.* 2019;21(7):933-939.

⁵⁶ Byron MJ, Baig SA, Moracco KE, Brewer NT. Adolescents’ and adults’ perceptions of ‘natural’, ‘organic’ and ‘additive-free’ cigarettes, and the required disclaimers. *Tob Control.* 2016;25(5):517-520.

⁵⁷ O’Connor RJ, Lewis MJ, Adkison SE, Bansal-Travers M, Cummings KM. Perceptions of “natural” and “additive-free” cigarettes and intentions to purchase. *Health Educ Behav.* 2017;44(2):222-226.

from combusted cigarettes to IQOS. Given that smokers perceive IQOS as presenting lower health risks than combusted cigarettes, and many smokers believe that cutting down on smoking reduces health risks, it is likely that smokers would expect at least some health benefit from substituting Heatsticks for some, but not all, of their combusted cigarettes. Because consumers need to switch completely to achieve the benefits of reduced exposure described in the modified risk claim, **postmarket surveillance should be conducted to ensure consumers understand that the benefits of reduced exposure cannot be achieved by continuing to smoke combusted cigarettes in addition to using IQOS.**

C. Tobacco Use Behavior and Impacts to the Population as a Whole

An assessment of the impact of an MRTP marketing authorization on the population as a whole is primarily a function of the relative health risks of the proposed product and the likelihood of tobacco use behavior change, including due to the modified risk marketing. Assessing the impact to the population as a whole includes an assessment of the potential impact of the product, including with the proposed modified risk information, on tobacco users and non-users if the product were to be authorized as an MRTP.

Several lines of evidence were provided to inform the assessment of the impact of the proposed MRTP on tobacco users and non-users, including abuse liability studies, pre- and post-market observational studies, and consumer perception studies evaluating the impact of the proposed modified risk claims. In addition, the applicant provided a population model of the potential impact of the proposed MRTP. A summary of these studies and conclusions are described below.

1. Impacts to Tobacco Users

Abuse Liability

The applicant conducted several studies that assessed the abuse liability and addictive potential of the IQOS system. The main findings from these studies are summarized below. A more detailed discussion and analysis can be found in the Behavioral and Clinical Pharmacology review.

Systemic Nicotine Exposure

Four single-use, randomized pharmacokinetic/pharmacodynamic (PK/PD) studies were conducted to assess and compare the rate and extent of nicotine uptake in participants using THS 2.2 compared to smoking own-brand cigarettes and NRT products. In the two Japanese studies, the primary nicotine exposure parameters⁵⁸ were similar between the THS 2.2 arm and the combusted cigarette (CC) arm. In the Irish and U.S. studies, mean values of the nicotine exposure parameters in the IQOS arm were lower than in the CC arm and lower than the THS 2.2 arm than the Japanese studies.

In the four reduced exposure studies, nicotine equivalents (NEQ)⁵⁹ were measured in urine to estimate nicotine exposure, since it reflects at least 80% of the daily nicotine uptake in smokers.⁶⁰ In general, the 24-hour NEQ urinary concentrations adjusted for creatinine were similar between THS 2.2 and CC arms

⁵⁸ The primary PK parameters in these studies were maximum nicotine plasma concentration, C_{max} , and area under the nicotine plasma concentration vs. time curve from time zero to the last observation, AUC_{0-last} .

⁵⁹ NEQ consists of nicotine and five of its major metabolites: nicotine-glucuronide, cotinine and its glucuronide, trans-3'-hydroxycotinine and its glucuronide.

⁶⁰ Wang J, Liang Q, Mendes P, Sarkar M. Is 24h nicotine equivalents a surrogate for smoke exposure based on its relationship with other biomarkers of exposure? *Biomarkers*, 2011;16(2):144-154.

for each of the four studies. In the U.S. study, NEQ was slightly lower after the use of THSm2.2 compared to the mCC arm; however, the differences were not statistically significant.

Product Use Topography

In the reduced exposure studies, topography was an exploratory outcome, measured using the HPT SODIM® device model SPA/M. Two types of sample holders were validated to accommodate THS 2.2 Heatsticks and standard combusted cigarettes (8.04 mm filter diameter). THS 2.2 topography is limited by its intrinsic properties, which limit the number of puffs to 14 and smoking duration to a maximum of 6 minutes. (b) (4)

Overall, switching from combusted cigarettes to THS 2.2 resulted in differences across a variety of topography metrics. Compared to the CC arm, participants in the THS 2.2 arm (1) took more puffs (three of four studies), (2) had a shorter smoking duration (two of four studies), (3) had a higher puff frequency (four of four studies), and (4) did not differ in total puff volume. The applicant attributed these differences to adaptation to the intrinsic properties of the new product as well as to differences in nicotine delivery, product satisfaction, ritual, sensory factors, and taste. Findings were similar for menthol and non-menthol flavor products.

Subjective Measures

The degree to which current smokers and non-smokers are likely to use the product and become addicted or dependent on it was evaluated by self-report questionnaires. Participants reported perceived effects of THS 2.2 on nicotine dependence and dependence symptoms (e.g., craving, withdrawal), reward/reinforcement following use, product valuation (i.e., hypothetical purchasing) compared to own-brand combusted cigarettes, and product misuse.

Craving, Withdrawal, Dependence: The Questionnaire of Smoking Urges – Brief (QSU-Brief) measures craving from two perspectives: 1) the intention and desire to smoke and anticipation of positive effects from smoking (positive reinforcement), and 2) the anticipation of relief from negative affect and nicotine withdrawal, and urgent and overwhelming desire to smoke (negative reinforcement). In the four PK/PD studies, relief from craving (QSU-Brief) showed a similar time curve following both THS 2.2 and CC arms: highest smoking urge prior to use, sharp decline following use, and continued decline to approach baseline over 12 hours. In the main comparison encompassing all time points, reductions in craving following product use showed no significant differences between the THS 2.2 and CC arms for all studies. In the four REX studies, relief from craving (QSU-Brief) did not differ significantly between the THS 2.2 and CC arms and remained stable throughout the study.

The Minnesota Nicotine Withdrawal Scale – Revised (MNWS) measures relief from withdrawal based, in part, on withdrawal symptoms identified in the Diagnostic and Statistical Manual of Mental Disorders (DSM) and the International Classification of Diseases – 10th Edition (ICD-10) and a question on craving. In addition to these validated items, the applicant included the symptom *impatient* to calculate the validated score. In the REX studies, no differences were found between study arms, at Days 5 or 90, on the MNWS questionnaire.

The Fagerström Test for Nicotine Dependence (FTND) is a test of physical dependence. In the two 90-day REX studies, FTND was administered at baseline and at the end of the ambulatory period (Day 90). No statistical analysis was conducted. No differences in dependence severity were found between the THS 2.2 and CC arms at Day 90.

Reinforcement: Reinforcing and aversive effects were measured using a self-report questionnaire (Modified Cigarette Evaluation Questionnaire, MCEQ) whose subscales include smoking satisfaction, psychological reward, aversion, enjoyment of respiratory tract sensations, and craving reduction. In the PK/PD studies, MCEQ was administered after product use; for these studies, MCEQ was a secondary outcome measure. In the REX studies, MCEQ was administered at the end of the day (8-11 pm) and data were exploratory and therefore descriptive.

In the PK/PD studies, THS 2.2 had significantly lower MCEQ ratings than combusted cigarettes. Compared to own-brand combusted cigarettes, THS 2.2 scored lower on four of five MCEQ subscales: Craving Reduction (2 studies), Enjoyment of Respiratory Tract Sensations (4 studies), Psychological Reward (1 study), and Smoking Satisfaction (4 studies). Scores on the Aversion subscale showed no difference between THS 2.2 and combusted cigarettes. In the REX studies, THS 2.2 had significantly lower ratings than combusted cigarettes, ranging from 0.7 to 1.3 point differences between study arms on Day 5 (end of confinement). THS 2.2 scored lower on four of five MCEQ subscales: Craving Reduction (two studies), Enjoyment of Respiratory Tract Sensations (one study), Psychological Reward (one study), and Smoking Satisfaction (three studies); scores on the Aversion subscale showed no difference between THS 2.2 and combusted cigarettes. In the two 90-day studies, no differences were found on any subscales on Day 90 (end of study). Findings were similar for menthol and non-menthol products.

Differences on the MCEQ subscales following a single use (PK/PD studies) and 5 days of confined use (REX studies), and a lack of differences after 90 days of use (REX studies) may reflect a learning or adaptation period to the new product.

Misuse

Product misuse may increase the nicotine exposure and/or quantity of use, thereby increasing THS 2.2 abuse potential. THS 2.2 misuse was assessed in the actual use study based on self-report, which is susceptible to missing or inaccurate data. Of 985 participants, 47 (4.8%) reported using Heatstick without the IQOS device; the majority (97.9%) lit the Heatstick like a combusted cigarette, and one participant chewed the Heatstick on one occasion. Only two participants (0.2%) reported using the IQOS device without Heatsticks; one participant used the IQOS device with marijuana on one occasion and one participant used it with combusted cigarettes on more than ten occasions.

The applicant also submitted a study of adult smokers' ability to understand and follow the instructions for using IQOS (PBA-06). The study consisted of one-on-one interviews in which participants were asked to demonstrate various tasks with IQOS (e.g., correctly inserting a Heatstick into the holder) and to answer open-ended questions about how to use IQOS. The study found that most participants (85%) understood that the IQOS holder should only be used with Heatsticks and not combusted cigarettes. Also, most participants (95%) understood that they should not light a Heatstick as they would do with a combusted cigarette.

Conclusion

Systemic nicotine exposure is similar after single and multiple uses of IQOS and combusted cigarettes, for both non-menthol and menthol products. Nicotine exposures appear sufficient to provide user

satisfaction, which may facilitate switching from combusted cigarettes to IQOS. In addition, self-reported symptoms of craving, withdrawal, and dependence were comparable in clinical studies of IQOS use compared with combusted cigarettes, and IQOS produces self-reported reinforcing effects reaching or close to levels of combusted cigarette reinforcement. In totality, the data support the conclusion that IQOS will likely have an addictive potential and abuse liability similar to combusted cigarettes.

This conclusion supports the potential for IQOS to be a viable replacement product for current smokers who stand to gain the benefits of reduced exposure by completely switching. On the other hand, the abuse liability of the product also poses a risk of addiction to non-users who may try the product, including youth. Accordingly, this evidence suggests the importance of preventing youth access and exposure to the product and its marketing.

Patterns of IQOS Use

The applicant conducted several observational studies that assessed IQOS use patterns among current tobacco users, both in pre-market and post-market settings. Some of the studies included some of the proposed modified risk information, while others did not. The design characteristics of these studies are summarized in Table 5 and the findings are presented below. A more detailed discussion and analysis can be found in the Epidemiology review.

Table 5. Description of pre- and post-market studies of IQOS use patterns among tobacco users

	Actual Use Study (PBA-07)	Whole Offer Test	Post-Market Online Cross-Sectional Study	Post-Market IQOS Purchaser Study
Study design	Longitudinal	Longitudinal	Cross-sectional	Longitudinal (though did not assess changes in individuals)
Location, time period	U.S., September 2015 - January 2016, 6-week observational period.	Japan, 2013 Italy, 2013 Germany, 2014 Switzerland, 2014 South Korea, 2015 4-week observational period.	Japan, September 2016	Japan, January-July 2016
Sample size	1,106	Japan - 638 Italy - 535 Germany - 377 Switzerland - 416 South Korea - 843	2,000 (5.2% response rate)*	~11,000
Attrition rate	12.4% (n=137) of participants included in the analyses did not have week 6 data.	All participants included in the analyses had data for all 4 weeks. The following proportion of participants did not complete the follow-up period: Japan – 11.1% Italy – 6.3% Germany – 14.9% Switzerland – 19.4% South Korea – 9.9%	N/A	Not reported

	Actual Use Study (PBA-07)	Whole Offer Test	Post-Market Online Cross-Sectional Study	Post-Market IQOS Purchaser Study
Population source	Market research consumer-based databases from across the U.S.	Market research consumer-based databases from each country.	Online panels that recruited from across Japan.	Adults from across Japan who purchased IQOS and registered their product in an online database.
Eligibility criteria	Aged ≥18 years; current daily smoker of regular and/or menthol cigarettes with no intention of quitting in the next 30 days (mean CPD = 10.2); expressed positive intention to use IQOS following exposure to labeling material that included modified risk information.	Aged ≥19 years; smoked ≥100 cigarettes in lifetime, smoke at least 3 cigarettes per day and smoked in past 7 days (mean CPD: Japan = 16.5; South Korea = 15.2; Italy = 12.7; Germany = 17.4; Switzerland = 17.3); expressed positive intention to use IQOS after trying one Heatstick. It is unclear whether the labeling material included modified risk information.	Aged ≥20 years and resided in Japan. Included cigarette smokers and non-smokers.	Adults that purchased and registered their IQOS device in the past 3 weeks and reported using ≥10 Heatsticks and/or cigarettes per week. Proportion of cigarette smokers unknown.
How IQOS was obtained	IQOS system and Heatsticks were provided for free (Marlboro and/or menthol).	IQOS system and Heatsticks were provided for free (Marlboro and/or menthol; only Marlboro was available in Italy and Germany).	Respondents were not provided IQOS. The device was purchased by the respondent or someone else.	Respondents were required to have purchased an IQOS device.
Assessment of IQOS and cigarette use	1-week baseline period to daily record cigarette smoking frequency in e-diary. 6-week observational period to record cigarette smoking and IQOS use in e-diary on a daily basis.	Self-report average number of cigarettes per day during enrollment interview. 4-week observational period to record frequency of cigarette smoking and IQOS use in paper and pencil diary on a daily basis.	One-time online survey that asked if respondents were current daily or some day users of cigarettes, “heat not burn” products, and other tobacco products.	Self-reported use of IQOS and combusted cigarettes in an online survey.

CPD = cigarettes per day.

*The study report stated that “38,235 contacts were made to reach the sample size.” It is not clear whether this large number of people was contacted to fill age, gender, and geographic location quotas that they were trying to meet during recruitment or because there was a high refusal rate among eligible individuals. Source: Sections 7.3.2, 7.3.3 of the PMTAs, March 16, 2017 amendment, and September 13, 2017 amendment.

Actual Use and Whole Offer Test Studies

The applicant conducted an actual use study (PBA-07) to assess near real-world use patterns of the IQOS system among adult daily cigarette smokers in the U.S. This pre-market observational study was conducted between September 2015 and January 2016 in eight U.S. cities. Potential participants were exposed to IQOS labeling and marketing that included some modified risk information and those that expressed a willingness to use the product regularly if they liked it were eligible to enroll. The Whole Offer Test (WOT) was an observational study designed to evaluate the likelihood that adult daily smokers in Asia (Japan, South Korea) and Europe (Italy, Germany, Switzerland) will switch from cigarettes to Heatsticks in near real-world conditions. Participants were exposed to pack design and

other branded materials; however, it is unclear from the protocol whether these materials included the modified risk information. In both studies, participants were provided with an IQOS system and Heatsticks free of charge and were instructed to use them and any other tobacco products containing nicotine *ad libitum*. The actual use study lasted for four weeks and the WOT lasted for six weeks.

Table 6 presents results for primary outcomes of these studies, which included the prevalence of initiating IQOS use, switching from combusted cigarettes to IQOS, and switching from IQOS back to combusted cigarettes. At the end of the observational period, the prevalence of initiating IQOS use (i.e., consuming ≥ 100 Heatsticks) was lowest in the U.S. at 33.8%. In the WOT, the proportion of participants who initiated IQOS use was highest in South Korea (76%) and Japan (61%). By the last week of the U.S. study, about 33% of those who initiated IQOS use, “switched” from combusted cigarettes to IQOS. It should be noted that the applicant’s definition of switching was Heatstick use accounting for at least 70% of the total number of combusted cigarettes and Heatsticks consumed in a week. This definition describes predominant IQOS use rather than complete switching (e.g., someone could reduce consumption from 2 packs per day to $\frac{1}{2}$ a pack per day and still be considered a switcher).

The applicant also reported the proportion of IQOS initiators who became “exclusive” IQOS users, defined as Heatsticks accounting for at least 95% of their total combusted cigarette plus Heatstick consumption in a week. In the U.S., 16% of those who initiated IQOS were considered to be exclusive IQOS users during the last week of the study, higher than what was observed in Europe, but lower than what was seen in the Asian countries. Finally, the prevalence of switching back to combusted cigarettes was highest in the U.S., where in the last week of the study about 15% of those who switched to IQOS had switched back to predominantly using combusted cigarettes.

Table 6. Prevalence of Heatstick initiation and switching at study end, by country

Country	Initiated IQOS use ^a among all smokers	“Switched” to IQOS ^b among those who “initiated” IQOS use	“Exclusive” IQOS use ^b among those who “initiated” IQOS use	“Switched” back to combusted cigarettes ^c among those who previously “switched” to IQOS
Actual Use Study (PBA-07)				
United States	33.8% (31.0%-36.7%) (N=1,106)	32.7% (27.8%-37.9%) (N=374)	16.3% (12.6%-20.7%) (N=374)	15.5% (10.6%-21.4%) (N=195)
Whole Offer Test (WOT)				
Japan	61.3% (57.4%-65.1%) (N=638)	46.3% (41.3%-51.4%) (N=391)	21.5% (17.5%-25.9%) (N=391)	0.0% (0.0%-2.0%) (N=180)
South Korea	76.3% (73.3%-79.1%) (N=843)	47.4% (43.5%-51.4%) (N=643)	20.1% (17.0%-23.4%) (N=643)	6.4% (4.0%-9.6%) (328)
Italy	36.1% (32.0%-40.3%) (N=535)	29.0% (22.7%-36.0%) (N=193)	13.0% (8.6%-18.5%) (N=193)	10.3% (3.9%-21.2%) (N=58)
Germany	50.1% (45.0%-55.3%) (N=377)	37.0% (30.1%-44.4%) (N=189)	15.3% (10.5%-21.3%) (N=189)	7.5% (2.5%-16.6%) (N=67)
Switzerland	49.5% (44.6%-54.4%) (N=416)	18.0% (13.0%-23.9%) (N=206)	7.8% (4.5%-12.3%) (N=206)	8.5% (2.4%-20.4%) (N=47)

Note: Estimates are the proportion of participants who met the criteria for each use pattern during Week 6 for the PBA-07 study and during Week 4 for the Whole Offer Test. Source: Sections 7.3.2 and 7.3.3.

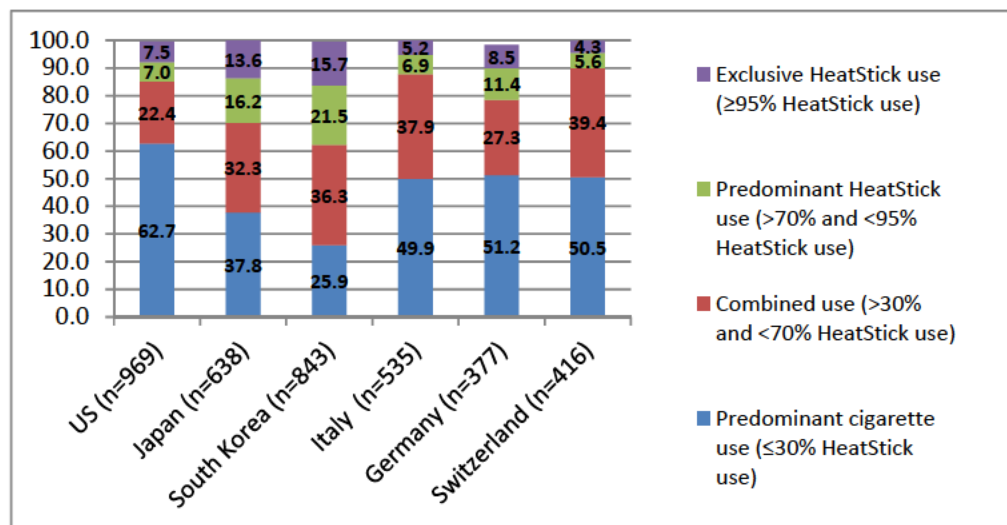
^a Initiated IQOS use is defined as consuming ≥ 100 Heatsticks during the observational period.

^b Switched to IQOS was defined as Heatsticks comprising $\geq 70\%$ of total combusted cigarette and Heatstick consumption during the last week of the observational period. “Exclusive” IQOS use was defined as Heatsticks comprising $\geq 95\%$ of total combusted cigarette and Heatstick consumption during the last week of the observational period.

^c “Switched” back to combusted cigarettes was defined as Heatsticks comprising $\leq 30\%$ of total combusted cigarettes and Heatsticks consumed in a week after having “switched” to Heatsticks in an earlier week.

Figure 6 presents the main IQOS use categories for all participants, regardless of whether they initiated IQOS use, during the last week of the observational period in the actual use study (U.S.) and WOT studies (non-U.S. countries). In the U.S., the majority of participants (62.7%) were classified as predominant combusted cigarette users in the last week and another 22% were considered combined users (Heatstick use comprised 30-70% of their total consumption). The applicant reported that 7.5% were “exclusive” Heatstick users ($\geq 95\%$ of total consumption), compared to 14-16% in Japan and South Korea. During the TPSAC meeting in January 2018, the applicant reported that 5.8% of participants in the U.S. actual use study were using Heatsticks 100% of the time during the last week of the observational period.

Figure 6. Percent of all participants in each main IQOS use category at the end of the PBA-07 and Whole Offer Test (WOT) studies, by country



Source: Sections 7.3.2 and 7.3.3 of the MRTPAs. Some bars do not add up to 100% due to participants who did not report using any Heatsticks or combusted cigarettes during the last week of each study, including 3 (0.3%) in the US, 1 (0.2%) in Japan, 6 (0.7%) in South Korea, 6 (1.6%) in Germany, and 1 (0.2%) in Switzerland. All participants in Italy reported using at least one Heatstick or cigarette during the last week of the study.

The actual use study also assessed change in product use per day and found that, across all groups, there was minimal change in total use of tobacco products (i.e., Heatsticks plus combusted cigarettes) between baseline and the observational period, suggesting that participants were replacing a proportion of their combusted cigarette use for Heatsticks rather than increasing their total tobacco product consumption.

In the U.S. study, at the end of the observational period, participants were asked about their likelihood to purchase the IQOS system “if the IQOS device were available for \$79.99 and a pack of Marlboro Heatsticks were available at a price comparable to a pack of Marlboro cigarettes.” In the overall sample (N = 987), nearly 20% of participants reported that they probably or definitely would buy IQOS. Findings were similar based on menthol/non-menthol preference, across age groups, and across baseline smoking rates. In a subsample of participants who used IQOS > 70% of the time (week 6, N = 138), nearly 50% reported they probably or definitely would buy IQOS.

Post-Market Survey in Japan

The applicant reported findings from an online post-market survey conducted in Japan in September 2016 among 2,000 adults aged 20 years and older. The study included both smokers and non-smokers. The aim of the study was to “assess the effects of IQOS” on the prevalence of tobacco product use in the Japanese adult population. In the September 2016 online cross-sectional survey from Japan, 3.7% of respondents reported currently using “heat-not-burn” tobacco products (2.3% used daily and 1.4% used less than daily). The prevalence of “heat-not-burn” product use was higher among those aged 20-29 (4.2%) and 30-39 (3.9%) than those aged 40-49 (1.5%) or ≥50 years (0.9%). Most current users of heat-not-burn products were using “Marlboro Heatsticks with IQOS device” (96.3%). The study indicated a high prevalence of dual use with cigarettes. Among respondents currently using heat-not-burn products, 84.9% also smoked cigarettes, most of them daily. For most heat-not-burn product users, heat-not-burn products comprised less than 30% of their average total daily tobacco consumption (i.e., cigarettes plus heat-not-burn products).

Post-Market Study of IQOS Purchasers in Japan

The applicant submitted a survey of self-reported use of IQOS and cigarettes in a market research panel of adult IQOS purchasers in Japan. Participants were aged 21 years and older, had purchased an IQOS device in the past 3 weeks, and registered their device in an online database. Participants must have also reported using at least 10 Heatsticks and/or combusted cigarettes per week. Although this study was a longitudinal panel where participants completed surveys weekly or monthly, the study did not look at changes in individuals over time. The applicant reported that the proportion of IQOS purchasers who were “exclusively” using IQOS (≥95%) increased from 52% in January 2016 to 65% in July 2016. The prevalence of exclusive IQOS use was much higher in this survey than the pre-market studies that observed about 7.5% exclusive IQOS use in the U.S. actual use study and about 13.6% exclusive IQOS use in the Japan site of the WOT. The applicant suggests that these discrepancies between pre- and post-market studies are the result of increasing popularity and awareness of IQOS that occurred post-market through word of mouth or other forms of communication. Reviewers note, however, that these discrepancies may also be attributable to the nature of the study design – those who take the initiative to register their device are likely to be a non-representative sample of all Japanese IQOS users and may be more motivated to become exclusive IQOS users.

It is also important to note a major difference between the policy environments of the U.S. and Japan that may influence the prevalence of switching to IQOS. In Japan, nicotine containing e-liquid is categorized as a pharmaceutical ingredient and is strictly controlled; therefore, nicotine-containing e-cigarettes are not as readily available as they are in the U.S. Consumers may be more likely to try using IQOS if non-cigarette tobacco products such as nicotine-containing e-cigarettes are not readily available.

Conclusion

The observational studies reported by the applicant suggest that dual use with combusted cigarettes is the predominant pattern of IQOS use, whereas exclusive use was relatively less prevalent. There was variability in these patterns across studies and countries. For instance, the proportion of users that used IQOS exclusively ranged widely from 7.5% in the U.S. actual use study to 65% in a post-market survey among IQOS purchasers in Japan. Because exclusive use is how individuals can reduce their exposure, these findings do not provide strong support for the potential benefit to the population as a whole. However, although dual use of IQOS and combustible cigarettes was commonly observed across the behavioral studies submitted, these studies were conducted over a relatively short-time frame and it is unclear whether dual use would be a sustained behavior or transition state. In addition, this data comes from studies where participants were not provided any modified risk information as well as from studies in which it was unclear the extent to which the modified risk information that participants were exposed to prior to enrollment was noticed by participants or whether such information impacted behavior. If the products were authorized as MRTPs, there would be explicit communication that reduced exposure results from “switching *completely* from conventional cigarettes to the IQOS system” (emphasis added). Therefore, the lack of strong positive support from this behavioral data should be balanced with these considerations.

Likelihood of Use After Exposure to Proposed Modified Risk Claims

The applicant conducted several studies to assess adult smokers’ intentions to try or use IQOS after exposure to its proposed modified risk claims. The findings from these studies are summarized below. More detailed description and analysis can be found in the Social Science review.

The applicant conducted a quantitative assessment of adult smokers’ and non-smokers’ responses to LLA materials with or without its proposed modified risk claims. Namely, these studies assessed: the reduced risk claims (PBA-05-RRC and PBA-05-RRC2), the reduced exposure claim (PBA-05-REC), and no claim (PMTA-05-NOC). As in section III.B, the following assessment of likelihood of use after exposure to a claim will focus on the reduced exposure claim, drawing on findings from the PBA-05-REC and PMTA-05-NOC studies.

Likelihood that current smokers will start using IQOS

In study PMTA05-NOC, where the LLA materials did not include any of the three proposed claims, many smokers expressed an intention to use IQOS, suggesting the potential for many smokers to switch to IQOS, which would be expected to benefit population health. For example, among smokers with no intention to quit smoking, 40-44% reported that they would “definitely” or “very likely”, and 31-39% said they would be “somewhat likely”, to try IQOS after they viewed the brochure, Heatsticks pack, or direct mail communication.⁶¹ Results were similar among smokers with an intention to quit. Furthermore, 26-33% of current smokers reported that, if they tried IQOS and liked it, they would “definitely” or “very likely” use it regularly, on an ongoing basis. It is important to note that self-reported intentions to use products can overestimate the likelihood of purchase, particularly when responses are unconstrained (i.e., when participants’ responses have no consequences that motivate them to reveal their true preferences). Although participants viewed price information about IQOS and Heatsticks in the applicant’s studies, they were not asked to actually make a choice between the product and money.

⁶¹ This excludes responses in a study condition in which participants viewed a Heatsticks pack that the applicant stated is “not intended for commercialization” (PMTA05-NOC Study Report, p. 3).

Looking across the studies that either did or did not include a claim, the applicant found no evidence that adding the reduced exposure claim to the LLA materials increased smokers' intentions to use IQOS. In studies in which smokers viewed the LLA materials with the reduced exposure claim, intentions to use IQOS regularly were slightly higher among smokers with no intention to quit, and intentions were slightly lower among smokers with an intention to quit. When compared with the "no-claim" study, neither of these differences was statistically significant.

These results fail to show a significant positive effect of the claim on smokers' intentions to use the product. However, the Social Science review noted limitations in the way the applicant analyzed its results that restricted its ability to make definitive conclusions about the proposed claims' effects on intentions to use IQOS. The relative impact of the claim notwithstanding, the interest in trying the product reported by a majority of smokers exposed to the products' LLA (either with or without a claim) supports the conclusion that authorization of these products with the reduced exposure claim would be expected to have a positive impact on population health.

Likelihood that smokers who may have otherwise quit smoking will instead use IQOS

The applicant's quantitative research found that approximately 30-40% of smokers classified as intending to quit smoking (i.e., planning to quit in the next 30 days or seriously considering quitting in the next 6 months) reported interest in trying or using IQOS. The implications of this finding are unclear. For instance, at least some smokers in the applicant's qualitative research appeared to view IQOS as a "step-down" product that they could use to lower their risk and help them ultimately quit smoking or quit using tobacco altogether.

Intention to quit smoking did not change for most smokers after viewing LLA materials with or without the proposed claims. Between 86-99% of smokers initially classified as intending to quit smoking continued to express an intention to quit after viewing LLA materials with or without the proposed claim. The applicant's research could not provide information about whether the slight reduction in intention to quit was caused by viewing IQOS LLA materials or whether it reflects low item reliability or testing effects.

Finally, as discussed above, smokers intending to quit perceived the health risks of using IQOS to be higher than those of quitting smoking with NRT. Also, as described above, after viewing LLA materials (with or without the claim) and SG Warnings or PMI Warnings, consumers perceived IQOS as a tobacco product that presents moderate risks of a wide range of tobacco-related diseases and health effects, suggesting that consumers would understand that using IQOS is more harmful than not using any tobacco products. In sum, the evidence does not suggest concern that IQOS would dissuade smokers from quitting.

Conclusion

Systemic nicotine exposure is similar after single and multiple uses of IQOS and combusted cigarettes, for both non-menthol and menthol products. Nicotine exposures appear sufficient to provide user satisfaction, which may facilitate switching from combusted cigarettes to IQOS. In addition, self-reported symptoms of craving, withdrawal, and dependence were comparable in clinical studies of IQOS use compared with combusted cigarettes, and IQOS produces self-reported reinforcing effects reaching

or close to levels of combusted cigarette reinforcement. In totality, the data support the conclusion that IQOS will likely have an addictive potential and abuse liability similar to combusted cigarettes.

In the U.S. actual use study submitted by the applicant, one-third of participants who were current cigarette smokers initiated IQOS use, yet the prevalence of complete switching was very low (5.8%). Based on this, the majority of TPSAC members did not think it was likely that U.S. smokers would switch completely to IQOS and, instead, thought it was moderately to highly likely that U.S. smokers would become long-term dual users of IQOS and combusted cigarettes. Although dual use of IQOS and combustible cigarettes was commonly observed across the behavioral studies submitted, these studies were conducted over a relatively short-time frame and it is unclear whether dual use would be a sustained behavior or transition state. It was unclear the extent to which the modified risk information that participants were exposed to prior to enrollment was noticed by participants or whether such information impacted behavior. Thus, although dual use was commonly observed across the behavioral studies submitted, this may have been in the absence of clear information that complete switching is necessary to achieve the exposure reduction benefits of the product.

It should also be noted that those who had achieved exclusive IQOS use were unlikely to revert to predominant combustible cigarette use during the study, indicating that for some smokers, IQOS is a viable replacement for cigarettes.

Although the applicant found no evidence that adding the reduced exposure claim to the LLA materials *increased* smokers' intentions to use IQOS, many smokers expressed high interest in the product and intended to try and use it after viewing LLA materials. In addition, viewing LLA materials with the proposed reduced exposure claim did not appear to reduce intentions to quit among smokers who initially expressed an intention to quit smoking. Together, these findings are supportive that marketing IQOS with a reduced exposure claim could appeal to current smokers who are most likely to benefit from their use, and this supports a likely benefit to population health.

2. Impacts to Non-Users of Tobacco

The impact on tobacco use behavior among current users must be considered alongside the potential effects on tobacco use initiation among non-users. The applicant assessed the potential impact of IQOS among current non-users by including adult former smokers and never smokers in their consumer perception studies. They also oversampled young adult never smokers (between their states' legal smoking age at the time of data collection and 25 years old) in order to learn about the potential effects of the proposed modified risk claims on youth. The applicant did not provide any direct data on the potential for use or appeal among U.S. youth. FDA examined published literature to identify studies with youth or young adult prevalence of IQOS use in countries where it is currently marketed. A summary of the relevant findings is presented below and provided in more depth in the Social Science and Epidemiology reviews.

Adult Former Smokers

In studies PBA-05-REC and PMTA05-NOC, the applicant examined former smokers' intentions to use IQOS after viewing LLA materials with or without the proposed reduced exposure claim. In these studies, some adult former smokers reported intending to use IQOS after viewing LLA materials, regardless of whether the materials included the proposed claim. When former smokers viewed LLA materials with no

claim, 5-7% said they would “very likely” or “definitely” try IQOS.⁶² When the LLA materials contained the reduced exposure claim, the comparable percentages were 3-6%. When examining the percentages of former smokers responding that they would “somewhat likely” try IQOS, there was also little evidence that the proposed claim increased the proportion of former smokers’ intending to use it. Specifically, when LLA materials contained no claim, 11-20% of former smokers said they would “somewhat likely” try IQOS, compared to 9-15% for the reduced exposure claim.

The applicant found limited evidence that adding the reduced exposure claim to the LLA materials may have increased former smokers’ intentions to use IQOS. Across studies in which former smokers viewed the LLA materials with the proposed claim, intentions to try IQOS were similar to those in the study in which they viewed LLA materials with no claim (4.2-6.3% vs. 6.3-6.5%, respectively⁶³). For intentions to use IQOS regularly, if one tries it and likes it, former smokers’ intentions were slightly higher in the studies in which participants viewed LLA materials with the proposed claim rather than without them (3.1-5.2% vs. 2.1-1.1%, respectively).

In sum, the results suggest some interest in trying the product among former smokers, but the addition of the claim did not appear to increase interest among this group. Accordingly, the results do not suggest that the products, if marketed with a reduced exposure claim, would generate a high level of interest among former smokers. This finding is consistent with a potential benefit to population health.

Adult Never Smokers

In studies PBA-05-REC and PMTA05-NOC, the applicant examined adult never smokers’ intentions to use IQOS after viewing LLA materials with or without the proposed exposure reduction claim. In these studies, relatively few adult never smokers reported intending to use IQOS after viewing LLA materials, regardless of whether the materials included the proposed claim. When never smokers viewed LLA materials with no claim, 0-1% said they would “very likely” or “definitely” try IQOS. When never smokers viewed the proposed reduced exposure claim, the comparable percentages were 0-2%. Intentions to try IQOS appear higher when including the percentages of never smokers who responded that they would “somewhat likely” try IQOS. However, these percentages do not appear to be any higher among people who viewed LLA materials with the proposed claim rather than without a claim. When viewing LLA materials with no claim, 4-7% of never smokers said they would “somewhat likely” try IQOS,⁶⁴ compared to 2-5% when viewing the LLA materials with the reduced exposure claim. For intentions to use IQOS regularly if one tries it and likes it, never smokers’ intentions were similar in the studies in which participants viewed LLA materials with the proposed claim rather than without it (0-1% vs. 0-2%, respectively).

In sum, the results suggest almost no interest in trying the product among adult never smokers, and the addition of the reduced exposure claim did not appear to increase interest among this group. Accordingly, the results do not raise concerns that the proposed MRTP would generate a high level of interest among never smokers. This finding is consistent with a potential benefit to population health.

⁶² This excludes responses in a study condition in which participants viewed a Heatsticks pack that the applicant stated is “not intended for commercialization” (PMTA05-NOC Study Report, p. 3).

⁶³ Results from PBA-05-REC and NOC studies, respectively, and ranges reflect brochure and Heatstick pack conditions where SG warning was used.

⁶⁴ This excludes responses in a study condition in which participants viewed a Heatsticks pack that the applicant stated is “not intended for commercialization” (PMTA05-NOC Study Report, p. 3).

Young Adult Never Smokers

The applicant's quantitative studies of consumer responses to IQOS LLA materials included oversamples of never smokers who were between their states' legal smoking age at the time of data collection and 25 years old (young adult never smokers). The summary below provides the findings for the PBA-05 studies, in which the applicant conducted a quantitative assessment of young adult never smokers' responses to LLA materials with or without the reduced exposure claim.

Relatively few young adult never smokers reported intending to use IQOS after viewing LLA materials, regardless of whether the materials contained the proposed claim. When young adult never smokers viewed LLA materials with no claim, 0-1% said they would "very likely" or "definitely" try IQOS. When young adult never smokers viewed the proposed reduced exposure claim, the comparable percentages ranged from 0-2%. As noted in FDA's PMTA TPL review for these products,⁶⁵ reviewers question the applicant's decision to define intentions as only those responding "definitely" or "very likely" while excluding "somewhat likely." Indeed, intentions to try IQOS appear higher when including the percentages of young adult never smokers who responded that they would "somewhat likely" try IQOS. However, these percentages do not appear to be any higher among people who viewed LLA materials with the proposed claim rather than without the claim. When viewing LLA materials with no claim, 7-10% of young adult never smokers said they would be "somewhat likely" to try IQOS, compared to 3-7% who viewed materials with the proposed claim.

Similar results were observed for intentions to use IQOS regularly if one tries it and likes it. Among young adult never smokers who viewed LLA materials with none of the proposed claims, 2% (in each study arm) responded that they would "definitely" or "very likely" use it regularly,⁶⁶ compared to 0-1% (in each study arm) who viewed the materials with reduced exposure claim. Some young adult never smokers responded that they would "somewhat likely" use IQOS, including 0-4% when LLA materials contained no claim and 1-2% when materials contained the proposed reduced exposure claim.

In terms of published literature, Brose et al.⁶⁷ reported on the use of "heat-not-burn" tobacco products in an online survey of approximately 13,000 people in Great Britain conducted in February-March 2017.²⁷ Current use of "heat-not-burn" products was slightly higher in young adults 18-24 years old (1.90%) than adults aged 25-34 years (1.22%), 35-44 years (1.03%), 45-54 years (0.67%) and ≥55 years (0.29%).

In sum, the evidence related to young adult never smokers suggests low interest in trying the product. In the applicant's studies, the addition of the claim did not appear to increase interest in trying IQOS. Accordingly, the results do not raise concerns that the proposed MRTTP would generate a high level of interest among young adult never smokers. This finding is consistent with a potential benefit to population health.

⁶⁵ FDA. PMTA Technical Project Lead Review (TPL). FDA Submission Tracking Numbers (STNs): PM0000424-PM0000426, PM0000479. Silver Spring, MD: U.S. Food & Drug Administration; 2019. <https://www.fda.gov/media/124247/download>

⁶⁶ This excludes responses in a study condition in which participants viewed a Heatsticks pack that the applicant stated is "not intended for commercialization" (PMTA05-NOC Study Report, p. 3).

⁶⁷ Brose LS, Simonavicius E, Cheeseman H. Awareness and use of 'heat-not-burn' tobacco products in Great Britain. *Tob Regul Sci.* 2018;4(2):44-50.

Youth

The applicant did not submit research studies directly evaluating the potential for youth uptake of IQOS. FDA identified several published studies of IQOS use to understand the extent to which youth reported use of the product in countries where IQOS is currently marketed. Tabuchi et al.⁶⁸ conducted an Internet survey in 2015, 2016, and 2017 among individuals aged 15-69 years in Japan to collect information on current use (i.e., any use in the previous 30 days) of IQOS, other heated tobacco products, e-cigarettes, and combustible cigarettes.²⁵ The prevalence of IQOS use was 2.0% among youth aged 15-19 years, lower than the prevalence in those aged 20 years and older. In 2017, Liu et al.⁶⁹ conducted an in-person survey in Italy among participants aged ≥ 15 years.²⁶ Participants were asked if they had ever tried IQOS. Those who had not tried IQOS were further asked if they intended to try it. Among 15-24-year-olds, ever use was 0.9% and intention to try IQOS among never triers was 1.9%.

During the January 2018 TPSAC meeting, members of the committee expressed concern about the applicant's omission of youth data. The applicant stated that it included oversamples of young adults in its quantitative studies as a way to learn about the potential effects of the proposed modified risk claims on youth. However, the applicant did not provide any data or scientific rationale to justify why we would expect the results for young adults to be comparable to youth. It is unknown whether the claim would affect youth non-users differently than young adult non-users, for instance.

Though data on young adult non-users is informative, there is no direct evidence that the proposed reduced exposure claim would affect youth non-users in the same way. In the absence of research on how the proposed claim affects youth perceptions and intentions, it is worth considering research on other modified risk claims, even though different claims may affect youth differently. One available study suggests that modified risk claims similarly impacted risk perceptions among youth and adults and affected susceptibility to use the product only among adults.⁷⁰ In particular, presenting youth with the statement "Suppose the FDA approves a label saying that Swedish snus is less harmful than cigarettes" caused youth to perceive Swedish snus as exposing users to less harmful chemicals and as presenting a lower risk of serious health problems.⁷¹ Although generalizability may be limited, such research is the best available direct evidence we currently have on youth and shows that, just as with adults, exposing youth to modified risk claims lowers their risk perceptions. Studies suggest that perceptions of risk predict tobacco product use among youth^{72,73} and adults.⁷⁴ Thus, even though the proposed reduced exposure claim did not increase never tobacco users' intentions to use IQOS in the applicant's study, it is still possible that exposing youth and young adult non-tobacco users to the proposed claim could

⁶⁸ Tabuchi T, Gallus S, Shinozaki T, Nakaya T, Kunugita N, Colwell B. Heat-not-burn tobacco product use in Japan: its prevalence, predictors and perceived symptoms from exposure to secondhand heat-not-burn tobacco aerosol. *Tob Control*. 2018;27(e1):e25-e33.

⁶⁹ Liu X, Lugo A, Spizzichino L, Tabuchi T, Pacifici R, Gallus S. Heat-not-burn tobacco products: concerns from the Italian experience. *Tob Control*. 2019;28(1):113-114.

⁷⁰ El-Toukhy S, Baig SA, Jeong M, Byron MJ, Ribisl KM, Brewer NT. Impact of modified risk tobacco product claims on beliefs of U.S. adults and adolescents. *Tob Control*. 2018;27:s62-s69.

⁷¹ El-Toukhy S, Baig SA, Jeong M, Byron MJ, Ribisl KM, Brewer NT. Impact of modified risk tobacco product claims on beliefs of U.S. adults and adolescents. *Tob Control*. 2018;27:s62-s69.

⁷² Song AV, Morrell HER, Cornell JL, et al. (2009). Perceptions of smoking-related risks and benefits as predictors of adolescent smoking initiation. *Am J Public Health*. 2009;99:487-492.

⁷³ Strong DR, Leas E, Elton-Marshall T, Wackowski OA, et al. Harm perceptions and tobacco use initiation among youth in Wave 1 and 2 of the Population Assessment of Tobacco and Health (PATH) Study. *Prev Med*. 2019;123:185-191.

⁷⁴ Brose LS, Brown J, Hitchman SC, McNeill A. Perceived relative harm of electronic cigarettes over time and impact on subsequent use. A survey with 1-year and 2-year follow-ups. *Drug Alcohol Depend*. 2015;157:106-111.

increase their risk of initiating use of IQOS by lowering their risk perceptions. Importantly, the IQOS PMTA authorization similarly noted potential for youth appeal and included requirements aimed at limiting youth access and exposure to help minimize the likelihood of unintended uptake among youth.

Conclusion

After viewing LLA materials with the proposed reduced exposure claim, some adult former smokers expressed interest in trying IQOS, but the addition of the claim did not appear to increase interest among this group. In addition, very few adult never smokers, including young adult never smokers, expressed interest in using the product. Adding the proposed claim to LLA materials did not appear to increase adult or young adult never smokers' or former smokers' intentions to use IQOS. TPSAC members thought the likelihood of former users re-initiating tobacco use with IQOS was low and while their views on the likelihood of never smokers becoming established IQOS users was somewhat mixed, the majority thought the likelihood was low to moderate. The applicant did not randomize participants to view LLA materials with or without the proposed modified risk claim, which makes it difficult to draw inferences about the impact of the claim.

In general, youth and young adult never tobacco users are at increased risk of initiating tobacco use, given that most tobacco use initiation occurs during youth and young adulthood. While most TPSAC members did not see the same potential for appeal and use with IQOS, they discussed the trajectory of youth uptake of e-cigarettes as an example of novel products that gained traction quickly among youth. The applicant did not submit research directly evaluating whether the proposed modified risk claim would increase youth uptake of IQOS; however, the applicant found no evidence that adding modified risk claims to the LLA materials increased young adult never smokers' intentions to use IQOS. Two published studies conducted in Italy and Japan provide two recent estimates of the prevalence of IQOS use among youth and suggest that in those countries, youth use of IQOS is low. As TPSAC discussed, it is unclear, however, if and/or how this might translate to youth use of IQOS in the U.S., particularly as it relates to marketing IQOS as an MRTP. Given that youth are at increased risk, generally, for initiating tobacco use and the uncertainty around the effect of modified risk information on youth use, it is critical that a marketing plan for any products that receive MRTP orders be designed to target tobacco users and prioritize preventing youth exposure. It is important to note that FDA's marketing authorization order for the IQOS system (PM0000424-PM0000426, PM0000479) includes requirements intended to help ensure that the marketing of the products will continue to be appropriate for the protection of the public health, taking into account initiation among non-users, particularly youth. This includes providing FDA with all advertising and marketing plans before disseminating them, including plans to restrict youth access and limit youth exposure to the products' labeling, advertising, marketing, and/or promotion. In addition, the applicant is required track and measure actual delivery of all advertising impressions, including among youth.

3. Population Health Impact Model (PHIM)

The applicant presents results from a Population Health Impact Model (PHIM) to assess the possible effects of the proposed MRTPs on health in the U.S. The PHIM models population health effects as a function of prevalence of product use in the population and risk of product use to the individual.

The initial population in the scenarios simulated in the model is representative of the U.S. in 1990, and a "null scenario" (in which the products are not introduced into the U.S. market) and a "new product scenario" (in which the products are introduced) are modeled for a twenty-year period. The applicant

presents results from an implementation of the model called the “Business Case” scenario. Some of the key assumptions for this scenario include:

- Within 10 years of being on the U.S. market, IQOS will come to be used by 17% of US smokers. Approximately 15% of users will be exclusive users and 2% will be dual users with combusted cigarettes.
- Projections from the Business Case scenario over a twenty-year period have approximately 30% of smokers being IQOS users.
- It is assumed that most transitions to the proposed new products will be at middle ages among current cigarette smokers. The applicant states that younger people will be less likely to use the product for reasons such as the cost of the device and that older people are in general less likely to switch to other products.
- The applications also state that never and former smokers would not be interested in the new products, based on information from PBA studies discussed earlier.
- Relative risk for individuals switching from cigarettes to the proposed new tobacco products is modeled as a function of f and disease-specific half-lives. Simulations were conducted with values of 0, 0.1, 0.15, and 0.3 for f , which represent reductions in exposure of 70% to 100% compared with cigarette smoking.

Results from a simulation of the Business Case with f values from 0.1 to 0.3 find a reduction of 70,000 to 90,000 deaths over a twenty-year period. In addition, the applicant presents a range of different sensitivity analyses in which rates of initiation, cessation, and dual use are varied, along with estimates of relative risk reduction.

The applicant concludes that the simulation results consistently showed reductions in cigarette smoking prevalence and tobacco-attributable mortality associated with the introduction of IQOS, both in the Business Case scenario and in a wide range of sensitivity analyses. The applicant states that parameter inputs that were shown to not produce a population health benefit in simulations were very implausible. The applicant thus concludes, “Overall, based on the modeling results and scenario specifications, introducing THS into the U.S. population appears to lead to a sizeable public health benefit in terms of reduced cigarette smoking and tobacco-related mortality. Variation in the model parameter estimates within reasonable ranges would not materially change these conclusions.”

The Business Case scenario projects that IQOS will come to represent a substantial proportion of the smoking market in the U.S., accounting for approximately 17% of users in 10 years and 30% of users in 20 years, with most of these users being exclusive users. The modeling section does not present empirical evidence to support this forecast. The section also presents very little information about product use from the use studies that are presented in other sections of the applications to support these assumptions. If uptake of the products by consumers is lower, takes more time, or is more likely to occur as part of dual use, then the magnitude of any population health effects would be expected to be reduced. Many of the projected effects are dependent on assumptions about the relative risks of IQOS; however, individual harm from exposure to exclusive or dual use with the proposed products may not follow a linear dose-response relationship.

The modeling approach and selected model inputs are very limited in their ability to represent and measure potential use of the products among young people and the consequent health outcomes. The modeling section provides very little justification and no specific empirical evidence to support its assumptions that individuals who do not currently smoke cigarettes would not be interested in using the

proposed products or that young people would not find them appealing. For example, the section's only specific statement about initiation and use among young people is that this segment of the population would be unlikely to use the products because of the cost of the device. Although not referenced in this section of the application, the data on behavioral intentions from the applicant's consumer perception study provides some justification for a more limited appeal to non-users. However, the introduction of electronic cigarette devices in the U.S. in recent years has demonstrated that it is difficult to predict with accuracy and certainty the levels and patterns of initiation and use of new tobacco products introduced into the marketplace.

Conclusion

The applicant presented results from a PHIM used to assess the possible effects of the proposed MRTPs on health in the U.S. and concluded that the simulation results consistently showed reductions in cigarette smoking prevalence and tobacco-attributable mortality associated with the introduction of IQOS. However, FDA finds the modeling approach and selected model inputs very limited in their ability to represent and measure potential use of the products and the consequent health outcomes. The projected population health effects may be overstated if specific assumptions about tobacco use behavior and risks are not realized in the actual population, such as the assumption that the majority of IQOS users will switch completely from combusted cigarettes rather than dual use. In addition, the relatively short projection period of 20 years and use of mortality as a health outcome does not allow for adequate consideration of the long-term health effects of tobacco use initiation among youth and young adults. It was also not clear from the modeling information included in the applications whether the forecasts presented in this section are dependent on marketing the products with modified risk claims. As such, it is not clear whether the projected estimates are to be interpreted as resulting from the introduction of the products into the marketplace through PMTA marketing orders or would also require authorization of the proposed MRTP claims. Given these limitations, the population modeling projections are not particularly informative to the overall assessment.

IV. Conclusions and Recommendations

A. Review Conclusions – Risk Modification Order Request

The applicant has requested a risk modification order under section 911(g)(1) of the FD&C Act to market these products as follows:

Modified Risk Claim #1:

"AVAILABLE EVIDENCE TO DATE:

- The IQOS system heats tobacco but does not burn it.
- This significantly reduces the production of harmful and potentially harmful chemicals.
- Scientific studies have shown that switching completely from conventional cigarettes to the IQOS system can reduce the risks of tobacco-related diseases."

Modified Risk Claim #2:

"AVAILABLE EVIDENCE TO DATE:

- Switching completely to IQOS presents less risk of harm than continuing to smoke cigarettes."

In order for FDA to issue a risk modification order under section 911(g)(1) of the FD&C Act, the applicant must demonstrate that the proposed modified risk tobacco product, as it is actually used by consumers, will:

- Significantly reduce harm and the risk of tobacco-related disease to individual tobacco users; and
- Benefit the health of the population as a whole taking into account both users of tobacco products and persons who do not currently use tobacco products.

In evaluating the benefit to health of individuals and of the population as a whole under section 911(g)(1) of the FD&C Act, FDA must take into account:

- The relative health risks the modified risk tobacco product presents to individuals;
- The increased or decreased likelihood that existing tobacco product users who would otherwise stop using such products will switch to using the modified risk tobacco product;
- The increased or decreased likelihood that persons who do not use tobacco products will start using the modified risk tobacco product;
- The risks and benefits to persons from the use of the modified risk tobacco product compared to the use of smoking cessation drug or device products approved by FDA to treat nicotine dependence; and
- Comments, data, and information submitted to FDA by interested persons (section 911(g)(4) of the FD&C Act).

Furthermore, FDA must ensure that the advertising and labeling of the MRTP enable the public to comprehend the information concerning modified risk and to understand the relative significance of such information in the context of total health and in relation to all of the tobacco-related diseases and health conditions (section 911(h)(1) of the FD&C Act).

To the extent possible, the assessment integrates the various threads of evidence regarding the product and its potential effects on health and tobacco use behavior, including tobacco use initiation, to determine both the net effect of the product on overall tobacco-related morbidity and mortality and the distribution of the benefits and harms across the population.

After conducting a thorough scientific review of the information contained in the MRTPAs; the recommendations from the Tobacco Products Scientific Advisory Committee; comments, data, and information submitted to FDA by interested persons; and other scientific information identified by the agency from other sources, I conclude that:

- With respect the risk modification order requests, the applicant **has not demonstrated** that, as actually used by consumers, the products sold or distributed with the proposed modified risk information will significantly reduce harm and the risk of tobacco-related disease to individual tobacco users and benefit the health of the population as a whole, taking into account both users of tobacco products and persons who do not currently use tobacco products.

In particular, I find that the claims “Scientific studies have shown that switching completely from conventional cigarettes to the IQOS system can reduce the risks of tobacco-related diseases.” and “Switching completely to IQOS presents less risk of harm than continuing to smoke cigarettes.” are not substantiated. These reflect the conclusions from reviewers from the four scientific disciplines that evaluated the modified risk claims (Toxicology, Epidemiology, Medical, and Behavioral and Clinical Pharmacology) and are consistent with the findings from the Tobacco Products Scientific Advisory Committee (TPSAC). Although the available scientific evidence shows that the IQOS system produces lower concentrations of many harmful and potentially harmful constituents (HPHCs) compared to cigarette smoke and the non-clinical data suggests a favorable toxicological profile of the IQOS system compared to combusted cigarettes, the overall body of evidence was not sufficient to demonstrate that completely switching from combusted cigarettes to the IQOS system reduces the risk of tobacco-related disease or harm. Although the non-clinical evidence suggests a lower toxic potential for IQOS, there were limitations in the design of these studies that created uncertainty in the interpretation of study findings, thereby limiting the conclusions that could be drawn from this evidence. In terms of the clinical studies, it should first be noted that the applicant provided no long-term epidemiological data to show risk reduction. Additionally, in the two 90-day clinical studies, the biomarkers of potential harm (BOPHS) measured did not change appreciably across continued smokers, complete switchers to IQOS, and smoking abstinence. The six-month clinical study resulted in some significant differences in BOPHS, but the clinical significance of these changes is unclear. In addition, the proposed claims are exceedingly broad in their reference to “tobacco-related diseases” and “harm” in general, which implicates both claim substantiation and consumer understanding. Cigarette smoking is a cause of many diseases and harms and the relationship between increased consumption and disease risk varies. In addition, the abuse liability of the IQOS system is not expected to be appreciably different than that of combusted cigarettes. Similar abuse liability signifies that the IQOS system can sustain addiction in nicotine-dependent populations and, in non-users, can have a similar risk of initiation and developing addiction as combusted cigarettes. Overall, the evidence is not sufficient to demonstrate substantiation of either of the claims about reduced risk of tobacco-related disease or harm. Relatedly, there is no direct clinical or epidemiological evidence of risk reduction, and the available evidence is insufficient to demonstrate that the product, as actually used by consumers, will significantly reduce harm and risk to individual users and benefit the health of the population as a whole. Thus, the 911(g)(1) order should be denied.

B. Review Conclusions – Exposure Modification Order Request

The applicant has also requested an exposure modification order under section 911(g)(2) of the FD&C Act to market these products as follows:

“AVAILABLE EVIDENCE TO DATE:

- The IQOS system heats tobacco but does not burn it.
- This significantly reduces the production of harmful and potentially harmful chemicals.
- Scientific studies have shown that switching completely from conventional cigarettes to the IQOS system significantly reduces your body’s exposure to harmful or potentially harmful chemicals.”

Given the different requirements under sections 911(g)(1) and 911(g)(2), exposure modification orders may be granted by FDA when the available evidence is not sufficient for a risk modification order. Specifically, FDA may issue an exposure modification order under section 911(g)(2) of the FD&C Act (the “special rule”) if it determines that the applicant has demonstrated that:

- Such an order would be appropriate to promote the public health;
- Any aspect of the label, labeling, and advertising for the product that would cause the product to be a modified risk tobacco product is limited to an explicit or implicit representation that the tobacco product or its smoke does not contain or is free of a substance or contains a reduced level of a substance, or presents a reduced exposure to a substance in tobacco smoke;
- Scientific evidence is not available and, using the best available scientific methods, cannot be made available without conducting long-term epidemiological studies for an application to meet the standards for obtaining an order under section 911(g)(1); and
- The scientific evidence that is available without conducting long-term epidemiological studies demonstrates that a measurable and substantial reduction in morbidity or mortality among individual tobacco users is reasonably likely in subsequent studies (section 911(g)(2)(A) of the FD&C Act).

Furthermore, for FDA to issue an exposure modification order, FDA must find that the applicant has demonstrated that:

- The magnitude of overall reductions in exposure to the substance or substances which are the subject of the application is substantial, such substance or substances are harmful, and the product as actually used exposes consumers to the specified reduced level of the substance or substances;
- The product as actually used by consumers will not expose them to higher levels of other harmful substances compared to the similar types of tobacco products then on the market unless such increases are minimal and the reasonably likely overall impact of use of the product remains a substantial and measurable reduction in overall morbidity and mortality among individual tobacco users;
- Testing of actual consumer perception shows that, as the applicant proposes to label and market the product, consumers will not be misled into believing that the product is or has been demonstrated to be less harmful, or presents or has been demonstrated to present less of a risk of disease than one or more other commercially marketed tobacco products; and
- Issuance of the exposure modification order is expected to benefit the health of the population as a whole taking into account both users of tobacco products and persons who do not currently use tobacco products (section 911(g)(2)(B) of the FD&C Act).

In making the determinations under section 911(g)(2) of the FD&C Act, FDA must take into account:

- The relative health risks the modified risk tobacco product presents to individuals;
- The increased or decreased likelihood that existing tobacco product users who would otherwise stop using such products will switch to using the modified risk tobacco product;
- The increased or decreased likelihood that persons who do not use tobacco products will start using the modified risk tobacco product;

- The risks and benefits to persons from the use of the modified risk tobacco product compared to the use of smoking cessation drug or device products approved by FDA to treat nicotine dependence; and
- Comments, data, and information submitted to FDA by interested persons (section 911(g)(4) of the FD&C Act).

In short, unlike the section 911(g)(1) standard, which requires scientific evidence showing actual risk reduction (e.g., a finding that the product, as actually used by consumers, *will significantly reduce* harm and risk to individual users; a finding that the product, as actually used by consumers, *will benefit* the health of the population as a whole), section 911(g)(2) establishes a lower standard, which allows FDA to issue an order when risk reduction has not yet been demonstrated but is reasonably likely based on demonstrated reductions in exposure (e.g., a finding that a reduction in morbidity or mortality among individual users is *reasonably likely* in subsequent studies; a finding that issuance of an order is *expected* to benefit the health of the population as a whole).

Furthermore, FDA must ensure that the advertising and labeling of the MRTP enable the public to comprehend the information concerning modified risk and to understand the relative significance of such information in the context of total health and in relation to all of the tobacco-related diseases and health conditions (section 911(h)(1) of the FD&C Act).

After conducting a thorough scientific review of the information contained in the MRTPAs; the recommendations from the Tobacco Products Scientific Advisory Committee; comments, data, and information submitted to FDA by interested persons; and other scientific information identified by the agency from other sources, I conclude that:

- With respect the exposure modification order request, the applicant **has demonstrated** that the products sold or distributed with the proposed modified risk information meet the standard under section 911(g)(2) of the FD&C Act, including that a measurable and substantial reduction in morbidity or mortality among individual tobacco users is reasonably likely in subsequent studies, and issuance of an order is expected to benefit the health of the population as a whole taking into account both users of tobacco products and persons who do not currently use tobacco products.

After conducting a thorough assessment of the scientific evidence, I find that “the IQOS system heats tobacco but does not burn it,” “this significantly reduces the production of harmful and potentially harmful chemicals,” and “scientific studies have shown that switching completely from conventional cigarettes to the IQOS system significantly reduces your body’s exposure to harmful or potentially harmful chemicals.” This determination is based on the substantial reduction across the constituents on FDA’s HPHC list, which demonstrates that, on the whole, as compared to combusted cigarette smoke, the process used to heat tobacco in the IQOS system significantly reduces the production of harmful and potentially harmful chemicals compared to cigarette smoke. The applicant also demonstrated that the magnitude of differences in biomarkers of exposure (BOEs) to 15 HPHCs when smokers switch completely to IQOS is substantial. The BOEs reduced reflect a range of chemical classes (e.g., carbonyls, aromatic amines, polycyclic aromatic hydrocarbons, nitrosamines) and toxicity classes (e.g., carcinogenic, cardiovascular, respiratory, reproductive). Although BOEs are not available for every constituent on the HPHC list, the comparative aerosol data provided demonstrate that many other HPHCs are significantly reduced compared to combusted cigarette smoke. It is reasonable to expect

that completely switching to the IQOS system from combusted cigarettes would lower exposure to these constituents as well.

Although the non-clinical and clinical studies included in these applications were not sufficient to demonstrate that switching completely lowers the risk of disease compared to combusted cigarette smoking and failed to meet the threshold for issuance of a risk modification order at this time, the totality of evidence presented suggests that a measurable and substantial reduction in morbidity or mortality among individual tobacco users is reasonably likely in subsequent studies. This determination predominantly stems from the substantial reduction in HPHCs relative to combusted cigarette smoke. Although some chemicals of potential concern (not on FDA's HPHC list) may be higher in IQOS users, the increase in these constituents does not impact the conclusion that the substantial reductions in HPHCs and findings from the toxicological evidence are reasonably likely to translate to lower risk of tobacco-related morbidity and mortality. The toxicological studies that indicated the potential for lower toxicity were based on the complete mixture of chemicals produced by the IQOS system, which would capture the impact of any increases in chemical concentrations relative to combusted cigarette smoke. In addition, when assessing the overall yield of chemicals on FDA's established list of HPHCs, along with chemicals of toxicological concern identified by the applicant not on FDA's HPHC list, the yields of potential carcinogens, respiratory toxicants, and reproductive/developmental toxicants were considerably lower in Heatstick aerosols compared with combusted cigarette smoke.

In terms of consumer understanding, the applications support the findings required for authorization. Actual consumer perception testing supports that consumer understanding is in line with the relative risks of the product that are reasonably likely. Importantly, consumers did not interpret the proposed claim to mean that the product causes no risk. After viewing product labels, labeling, and advertising with the reduced exposure claims, on average, consumers perceived IQOS as a product with moderate risks of a range of tobacco-related diseases and higher in risk than quitting smoking and using nicotine replacement therapy instead. After viewing product labels, labeling, and advertising with the reduced exposure claims, on average, consumers also perceived IQOS as a product that is lower in risk than cigarettes, although exposure to the claim did not appear to have a substantial impact on these perceptions. The novel design of the product may contribute to these risk perceptions in the same way that many consumers perceived that e-cigarettes were a less harmful alternative to cigarettes when their use was becoming more common.⁷⁵ FDA considered whether these risk perceptions are problematic. As noted above, although the studies in the applications were not sufficient to support the issuance of a risk modification order at this time, the totality of the evidence supports that risk reduction is reasonably likely to be demonstrated in subsequent studies. In other words, consumer understanding is in line with the relative health risks of the product that are reasonably likely.

Under section 911(g)(2)(B)(iii), to issue an exposure modification order FDA must find that testing of actual consumer perception shows that, as the applicant proposes to label and market the product, consumers *will not be misled* into believing that the product *is or has been demonstrated* to be less harmful, or *is or has been demonstrated* to present less of a risk of disease than one or more other commercially marketed tobacco products. FDA interprets this to mean finding that consumers do not hold inaccurate beliefs or are not misled regarding the definitiveness of the evidence regarding the relative risks or harm of the product. As noted above, testing of actual consumer perception showed

⁷⁵ Pepper JK, Brewer NT. Electronic nicotine delivery system (electronic cigarette) awareness, use, reactions and beliefs: a systematic review. *Tob Control*. 2014 Sep;23(5):375-84.

that consumer understanding is in line with the relative health risks of the product that are reasonably likely and the current state of the evidence.

FDA considered whether including a disclaimer on product labeling and advertising would improve consumer understanding (e.g., improve understanding that although risk reduction is reasonably likely, it has not yet been demonstrated in scientific studies). Specifically, as part of its consumer perception study, the applicant tested the impact of a disclaimer (as part of its “PMI warning”) that states, “It has not been demonstrated that switching to the IQOS system reduces the risk of developing tobacco-related diseases compared to smoking conventional cigarettes.” However, as described in the body of the review, the study design limited the inferences that can be drawn from the study findings. Moreover, the currently available evidence suggests that, in general, disclaimers on tobacco products are often limited in their effectiveness.^{76,77,78} Accordingly, I do not expect that the disclaimer would improve consumer understanding. As noted above, testing of actual consumer perception shows that as the applicant proposes to label and market the product (without a disclaimer), consumers will not be misled about the current state of the evidence regarding the relative health risks of the product. Overall, the available evidence demonstrates that consumers generally understand the relative health risks of the product that are reasonably likely, which would be expected to impact behavior in a way that promotes public health.

One consumer misperception uncovered by the applicant’s studies was the perception that IQOS is less addictive than combusted cigarettes. To address this, FDA’s marketing authorization order for the IQOS system (PM0000424-PM0000426, PM0000479) requires inclusion of the warning statement “WARNING: This product contains nicotine. Nicotine is an addictive chemical.” on the package labels of all Heatsticks packs and on all kits containing Heatsticks packs as well as in all advertisements for such products and kits. In addition, the applicant did not assess what smokers understand about the health effects of *partially* switching from combusted cigarettes to IQOS, which would not be expected to result in the benefits of exposure reduction. As described below, postmarket surveillance should assess the extent to which consumers continue to understand the proposed modified risk information, including that the benefits of reducing exposure to harmful and potentially harmful chemicals require complete cessation of combusted cigarette smoking.

The available scientific evidence demonstrates that the issuance of an exposure modification order for IQOS would be appropriate to promote the public health and is expected to benefit the health of the population as a whole, taking into account both users of tobacco products and persons who do not currently use tobacco products. After viewing labels, labeling and advertising (LLA) materials with the exposure reduction claim, many smokers expressed high interest in IQOS and intended to use it. Although some former smokers expressed interest in IQOS, the addition of the claim did not appear to increase interest among this group. In addition, very few never smokers expressed interest in IQOS or intended to use it. Although dual use of IQOS and combustible cigarettes was commonly observed across the behavioral studies submitted, this was in the absence of clear information that complete switching is necessary to achieve the benefits of the product. The proposed MRTP claim informs consumers that complete switching from cigarettes to IQOS significantly reduces exposure to HPHCs.

⁷⁶ Baig SA, Byron MJ, Lazard AJ, Brewer NT. “Organic,” “natural,” and “additive-free” cigarettes: comparing the effects of advertising claims and disclaimers on perceptions of harm. *Nicotine Tob Res.* 2019;21(7):933-939.

⁷⁷ Byron MJ, Baig SA, Moracco KE, Brewer NT. Adolescents’ and adults’ perceptions of ‘natural’, ‘organic’ and ‘additive-free’ cigarettes, and the required disclaimers. *Tob Control.* 2016;25(5):517-520.

⁷⁸ O’Connor RJ, Lewis MJ, Adkison SE, Bansal-Travers M, Cummings KM. Perceptions of “natural” and “additive-free” cigarettes and intentions to purchase. *Health Educ Behav.* 2017;44(2):222-226.

Finally, the currently available evidence suggests that youth uptake of IQOS is currently low in countries where it has been measured. However, given that IQOS is still a relatively new product, the uptake and use patterns among youth in these markets, or any other market that may start selling IQOS, is unclear. Given that youth are at increased risk, generally, for initiating tobacco use and the uncertainty around the effect of modified risk information on youth use, it is critical that any marketing plans be designed to prioritize preventing youth exposure. FDA's marketing authorization order for the IQOS system (PM0000424-PM0000426, PM0000479) includes postmarket requirements to help ensure that youth exposure to tobacco marketing is being minimized. This includes informing FDA of all advertising and marketing plans prior to dissemination, implementing plans to restrict youth access and limit youth exposure to the products' labeling, advertising, marketing, and/or promotion, and requiring the applicant to track and measure actual delivery of all advertising impressions, including among youth. In addition, as described below, postmarket surveillance and studies should be conducted to monitor youth awareness and use of the IQOS system to ensure that marketing of the products as MRTPs will not have the unintended consequence of leading to increased use of these products among youth.

Section 911(g)(2)(C)(i) of the FD&C Act provides that an MRTP exposure modification order shall be limited for a term of not more than 5 years. I recommend authorization for a period of 4 years, given that these would be the first MRTP authorizations issued by the Agency for a novel tobacco product. The IQOS system has only been on the U.S. market for a limited period of time and has only been marketed internationally for a few years. The greater uncertainty associated with such a novel product warrants additional caution. Although this review has found that an exposure modification order for the products would be appropriate to promote the public health and is expected to benefit the health of the population as a whole, that determination may change over time as a function of how the products are actually used by consumers. Therefore, monitoring use of the IQOS system with Heatsticks in terms of uptake, dual use, and complete switching should be required, including the potential for initiation among youth. As described below, postmarket surveillance and studies must include an assessment of MRTP users' behavior and understanding over time. A 4-year period is a reasonable amount of time to assess whether there is appropriate consumer understanding and to generate preliminary data on behavior in postmarket surveillance and studies to assess whether the standard continues to be met and whether the order should be renewed.

C. Environmental Impact

A finding of no significant impact (FONSI) was signed by Luis Valerio, Ph.D. on June 29, 2020. The FONSI was supported by an environmental assessment prepared by FDA on June 29, 2020.

D. Postmarket Surveillance and Studies (PMSS)

I recommend that the following language be included in the marketing authorization:

Under section 911(g)(2)(C)(ii) of the FD&C Act, an order under 911(g)(2) is conditioned on the applicant's agreement to conduct postmarket surveillance and studies in order to "determine the impact of the order on consumer perception, behavior, and health, and to enable the [FDA] to review the accuracy of the determinations upon which the order was based in accordance with a protocol approved by the [FDA]."

I. PMSS Content

MRTP Use Behavior and Consumer Understanding and Perception

After receiving authorization, the determination of whether the tobacco products that are the subject of this order continue to satisfy the requirements of section 911(g)(2)(A) and (B), is driven, in part, by use behavior. In your applications, you describe plans for postmarket studies, including cross-sectional surveys and behavioral cohort studies. In your behavioral cohort study, monitoring use of the products that are the subject of this order in terms of uptake, dual use, and complete switching is required. In particular, your PMSS must assess the extent to which new MRTP users were never, former, or current smokers, or other tobacco product users before initiating the MRTPs and the extent to which new users of the MRTPs become exclusive IQOS users, dual users with combusted cigarettes or other tobacco products, or transition to combusted cigarette smoking over time. These studies should be designed to observe behavior over a sufficient period of time to examine, for instance, the extent to which dual use of IQOS and combusted cigarettes is a transitional versus stable pattern of use.

For your proposed cross-sectional surveys, given the novelty of these products and the uncertainty related to the impact of modified risk information on youth, your studies must be designed to monitor individuals under the age of 18 to assess: (a) youth awareness of IQOS, to evaluate how effectively your marketing is limiting unintended exposure to youth, and (b) youth use of the IQOS system, to help ensure that marketing of the MRTPs does not have unintended consequences for youth use. Your surveys must also monitor young adults below the legal age to purchase tobacco products (i.e., ages 18-20).

Your studies must also include an assessment of consumers' understanding of the claim and perceptions of the products. In particular, PMSS must assess the extent to which users of these products understand that reducing their exposure to harmful and potentially harmful chemicals is relative to smoking, as described in the modified risk information, and that current smokers must use the IQOS system exclusively and stop smoking. Thus, current smokers who take up IQOS, must understand that they should switch completely to IQOS and stop smoking and that cutting down on combusted cigarettes per day while using IQOS is not sufficient. Other tobacco users who switch to IQOS must understand that the reduction in harmful and potentially harmful chemicals is relative to combusted cigarette smoking and not to other types of tobacco use.

Your studies must have clear research objectives, including assessing whether the modified risk tobacco products are leading to changes in product use behaviors that are expected to benefit population health. Your protocol must include a statistical analysis plan describing, among other things, how you plan to conduct inferential statistical analyses to address these objectives.

In addition, FDA has determined that assessing the impact of your MRTP orders on uptake of the products requires surveillance of MRTP sales and distribution, which provide information to assess tobacco consumption at the population level. Your PMSS protocols must describe procedures for monitoring and reporting MRTP sales and distribution in the U.S. by product, major metropolitan areas, and channels where the products are sold (e.g., IQOS stores and kiosks, convenience stores, food and drug stores, internet and digital retailers, tobacco specialty shops). Your annual PMSS report must include:

- U.S. sales and distribution of the tobacco products by quarter since the date of issuance of your modified risk granted orders (for the initial reporting period) or the previous reporting period (for all reports that follow), including, for each MRTPA STN, total U.S. sales and distribution reported in dollars and units, and broken down by major metropolitan areas, and channels where the products were distributed and sold during the reporting period (e.g., IQOS stores, convenience stores, food and drug stores, internet and digital retailers, tobacco specialty shops).

- A brief synthesis and summary of the sales and distribution data for the initial reporting period or the previous reporting period (for all reports that follow), including annual and quarterly growth rate (percent change) in total U.S. sales and distribution of the tobacco products for each MRTPA STN, post-MRTP authorization.

MRTP Use and Health Risk - Toxicology

Although your applications demonstrated that switching completely from combusted cigarettes to the IQOS system would, in general, significantly reduce exposure to harmful or potentially harmful chemicals, there were some chemicals that were higher in Heatstick aerosol than in combusted cigarette smoke. Additional research must be conducted to better characterize the potential impact of these exposures. In your applications, you reported computational toxicology predictions on chemicals found in higher levels in Heatstick aerosols than in reference combusted cigarette smoke. However, your applications lacked details of the quantitative structure-activity relationship (QSAR) modeling prediction results including, information to judge reliability of the modeling results, information on how you made interpretations of the model predictions, and a description of the training sets used in the models and why they are appropriate for tobacco constituents to predict adverse effects at the endpoints that were tested. An adequate computational toxicology assessment of Heatstick aerosols must be conducted in order to predict potential adverse effects in users before toxicity may be evident.

Given that the chemicals analyzed by QSAR are found in higher levels in Heatstick aerosols than in reference combusted cigarette smoke and that Heatsticks are novel tobacco products for which long term health consequences have not been established, you must conduct a rigorous computational toxicology study using a battery of genotoxicity and carcinogenicity models (modeled endpoints: in vitro bacterial mutagenicity, mammalian cell mutagenicity, clastogenicity, rodent carcinogenicity) that have been validated in the published literature. A well-designed computational toxicology study must use both structure-activity-relationship (SAR), as well as QSAR models, and provide a full explanation of the computational basis for each prediction from the models. This includes probabilistic information of the prediction from a statistical model (i.e., probability of being positive), how the predictions were interpreted, model training set information including structurally similar compounds in the training set to the query compound, information on external validation testing and applicability domain of the models to understand reliability of the results for assessing the tobacco compounds.

MRTP Use and Health Risk – Serious and Unexpected Adverse Experiences

In order for FDA to determine whether the tobacco products that are the subject of this order continue to be appropriate to promote the public health and continue to be expected to benefit the health of the population as a whole taking into account both users of tobacco products and persons who do not currently use tobacco products (section 911(g)(2)(A-B)), your PMSS must include ongoing surveillance of all adverse experiences including those that are both serious and unexpected associated with the use of the MRTPs. These experiences may become known to you through any source, including a customer complaint, request, or suggestion made as a result of an adverse experience; or tobacco product defect, or failure, reported to you, or identified in the literature or media. Your PMSS protocols must include procedures for monitoring and analyzing adverse experiences and your annual PMSS report must include:

- A summary of reported serious and unexpected adverse experiences for the tobacco products, which includes a listing of all serious and unexpected adverse experiences during the reporting period and a cumulative list, including all serious and unexpected adverse experiences

previously reported. The summary must be accompanied by an analysis of the reports and a statement of any changes to risk information related to the products including nature, frequency, and potential aggravating factors.

In addition, the PMTA order for your tobacco products, issued on April 30, 2019, require you to report to the FDA all adverse experiences that are both serious and unexpected and your analysis of the association between the adverse experience and the tobacco product within 15 calendar days after the report is received by you. These experiences may become known to you through any source, including a customer complaint, request, or suggestion made as a result of an adverse experience, tobacco product defect, or failure, reported to you, or identified in the literature or media. We request that when submitting such reports, you reference both your PMTAs and your MRTPAs for these products. Your information should be submitted with a cover letter that includes the following text in the subject line: **SERIOUS UNEXPECTED ADVERSE EXPERIENCE REPORT FOR STNs PM0000424-PM0000426 and PM0000419 and MR0000059-MR0000061 and MR0000133.**

For purposes of this reporting, *serious adverse experience* means an adverse experience that results in any of the following outcomes:

- Death;
- A life-threatening adverse event;
- Inpatient hospitalization or prolongation of existing hospitalization;
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions;
- A congenital anomaly/birth defect; or
- Any other adverse experience that, based upon appropriate medical judgment, may jeopardize the health of a person and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition.

For purposes of this reporting, *unexpected adverse experience* means an adverse experience occurring in one or more persons in which the nature, severity, or frequency of the experience is not consistent with:

- The known or foreseeable risks associated with the use or exposure to the tobacco product as described in the PMTA (including the results of human subject investigations) and other relevant sources of information, such as postmarket reports and studies;
- The expected natural progression of any underlying disease, disorder, or condition of the person(s) experiencing the adverse experience and the person's predisposing risk factor profile for the adverse experience; or
- The results of nonclinical laboratory studies.

Surveillance of New Research Study Findings on the MRTPs and Consumer Perception, Behavior, or Health

In order for FDA to determine whether the tobacco products that are the subject of this order continue to be appropriate to promote the public health and continue to be expected to benefit the health of the population as a whole, your PMSS must include surveillance of new research study information about the MRTPs and consumer perception, behavior, or health. In particular, your PMSS protocol must include procedures for monitoring and assessing previously unreported (new) findings both in published or unpublished studies conducted by you or on your behalf and in published or otherwise available studies regarding the MRTPs and consumer perception, behavior, or health. Your annual PMSS report must include:

- A summary of significant findings about the tobacco products from research studies conducted by you or on your behalf, whether or not such studies were specifically required under this order. A summary of significant findings in publications not previously reported and full copies of the articles. This must include any new scientific data (published or otherwise) on the MRTPs and consumer perception, behavior, or health.

Modeling the Impact of the MRTP on Population Health

In order for FDA to determine whether the tobacco products that are the subject of this order continue to be appropriate to promote the public health and continue to be expected to benefit the health of the population as a whole, your PMSS must include computational modeling of the impact of the MRTPs on population health. Such modeling must incorporate data and information collected through PMSS, including the percentage of former smokers who start using IQOS; the percentage of current smokers who start using IQOS and become dual users; the percentage of current smokers who switch completely to IQOS; the percentage of youth and young adults below the legal age of purchase who start using IQOS; and the percentage of individuals who start using IQOS and then initiate or re-initiate combusted cigarette smoking. Postmarket modeling must incorporate the latest information on acute and long-term health effects of using IQOS relative to combusted cigarette smoking in order to assess the short and long-term population health impacts of the marketing. Your annual PMSS report must include:

- A description of the methodological approach used in the model;
- A copy of the model or its underlying code, such that FDA can independently run and verify the model inputs and outputs;
- A description of all model inputs, including the justification for input values and how they were derived from postmarket data and information; and
- A summary of the modeling results and their implications for assessing whether the MRTPs continue to be appropriate to promote the public health and continue to be expected to benefit the health of the population as a whole.

II. Submitting PMSS Protocols and Reports

As required under section 911(g)(2)(C)(ii) of the FD&C Act, your modified risk order is conditioned on your agreement to conduct PMSS under an approved protocol, and to submit the results for FDA to determine the impact of the order and review the accuracy of determinations on which the order is based. Within 30 days of receiving this notice, you must submit your agreement to conduct PMSS and complete protocols for your PMSS. Label your submission clearly as a “PMSS Protocol,” and reference your MRTPA Submission Tracking Numbers (STNs). If you have more than one protocol, submit each protocol as a separate submission. If applicable, each protocol should include the name(s) of the principal investigator(s) and materials that demonstrate the relevant professional credentials and training that qualify them to lead the study. Within 60 days of receipt of the protocol(s), FDA intends to review the protocol(s) and evaluate if the principal investigator proposed to be used in the surveillance has sufficient qualifications and experience to conduct the surveillance and if the protocol(s) will result in collection of data or other information that has the potential to enable FDA to accurately determine the impact of the order on consumer perception, behavior and health and to review of accuracy of the determinations upon which the order was based, pursuant to section 911(g)(2)(C)(ii) of the FD&C Act. FDA will notify you of and provide opportunities to address, any deficiency in the submission. If the PMSS protocol is amended subsequent to FDA approval, FDA must receive the amended protocol promptly. For protocol amendments that are administrative in nature (e.g., corrections in punctuation or titles), the amended protocol must be received by FDA within 30 days of the update. For protocol

amendments that seek to modify the study design (including endpoints, sites, questionnaires, methodology, etc.) or other scientific parameters, you may not initiate the change until you receive FDA approval.

As part of the requirement to conduct PMSS, you must initiate and conduct your PMSS per the timeframes established in your protocols and approved by FDA. Note that for PMSS that involve human subjects, the anticipated start date for each study must account for the time required for securing IRB approval, as needed. In addition to specifying the start date, your protocols must contain timelines for completion of major study milestones including, as applicable, the start and completion of participant recruitment, initiation of data collection (per wave, if applicable), completion of data collection, analysis, and report writing. If you deviate from these timelines, we request that you report the deviation within 30 days to FDA.

Section 911(g)(2)(C)(iii) requires that the results of the PMSS be submitted on an annual basis. These reports must be identified as “PMSS Report”, and the MRTPA STNs should be referenced for each report. The PMSS Report must indicate the beginning and ending date of the period covered by the report and must include accomplishments since the last reporting period. For quantitative updates on studies in progress (e.g., participant accrual), reports should describe both interim (since the last reporting period) as well as cumulative (since study initiation) accomplishments. The PMSS Report describing studies in progress must describe the status of PMSS, including, as applicable, the status of recruitment, data collection, and analysis; a summary of the study milestones achieved and any deviations from the approved timelines in the protocol; a summary of protocol amendments; and a summary of any preliminary analyses conducted. Once a study is completed, the PMSS Report should include the complete final study report.